THE

# AMERICAN JOURNAL

# OF THE MEDICAL SCIENCES

MAY, 1936

## ORIGINAL ARTICLES.

### TREATMENT OF PERNICIOUS ANEMIA WITH INTRAMUSCULAR INJECTIONS OF A HIGHLY CONCENTRATED SOLUTION OF LIVER EXTRACT.

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This report deals with the results observed in the treatment of 33 patients with pernicious anemia by means of intramuscular injections of a highly concentrated and refined extract of liver. The extract, so concentrated that 1 cc. contains the active principle derived from 100 gm. of liver, was prepared by Dr. Guy W. Clark, of the Lederle Laboratories, and was supplied for the purposes of this study as early as July, 1934.

Of the patients to be considered, 28 first received treatment when their red blood cell levels were below 3,500,000, having received no liver treatment for at least several months previously. In the majority no previous liver treatment had been used at any time. It has been possible to observe 26 of these patients under treatment with the same liver extract during periods varying in duration up to 1 year after their red blood cell levels had reached or passed 4,500,000 in order that their maintenance requirements might be determined.

In addition to the 28 patients in whom treatment was begun during relapse, 5 others have received injections of the 1 cc. material for slightly more than 1 year. The 5 patients were selected because each had been previously maintained on intramuscular injections of 3 cc. (Lederle) of liver extract prepared from 100 gm. of liver

for from 1 to 2 years during which time their maintenance requirement was found to be somewhat greater than that of the average of the patients under observation, as previously reported. It was believed that such a selection of patients would favor a more critical test of the efficiency of the new material.

Potency of the 1 cc. extract was demonstrated in 25 of the 28 patients treated during relapse by means of reticulocyte counts made daily on all patients in so far as it was possible. Ten of the patients were not admitted to the hospital for treatment and it was not always feasible to have them return daily for observation. The reticulocytes were counted in dry blood film preparations made on coverslips coated with a dry film of 0.5% alcoholic solution of cresyl blue as used in previous studies.[1] The effective or erythrocyte-producing potency of the extract was demonstrated, as previously advised,[2,3] by observation of erythrocyte production during a period usually of 4 weeks following the institution of therapy during relapse and by determination of the required amount of liver extract to maintain the blood in normal condition during sufficiently long periods of time to serve such a purpose. Periods of ½ year or longer are considered preferable for this purpose. Of the 28 patients first treated during relapse, 16 have been followed for from ½ to 1 year from the time the red blood cell levels had reached 4,500,000 and, therefore, serve as satisfactory cases to demonstrate the maintenance requirements along with the 5 cases reported only for that purpose.

**Results of Treatment During Relapse.** In Table 1 are recorded data obtained in 28 patients first treated during relapse. In those patients in whom blood studies included reticulocyte counts the highest count is recorded together with the day following the onset of therapy upon which this was observed. The magnitude of the reticulocyte response has varied considerably in the blood of the individuals of the groups classified according to the various initial erythrocyte levels, as is to be anticipated from previously reported observations.[2] Although the amount of liver extract injected for treatment during relapse and the method of its use has varied considerably in this group, it is obvious that this has had little influence upon the magnitude of the reticulocyte rise, although it has influenced the rate of their production.

Erythrocyte production was slower during the first 2 weeks of treatment in the 3 patients treated with small daily doses than it was in those receiving larger initial doses, whereas those receiving minimal amounts of material (2 cc.) during the first 4 weeks tended to produce erythrocytes less rapidly toward the end of this period than did those who received a greater amount of material, regardless of whether or not the material was given in daily small doses or larger less frequent ones.

The rate of erythrocyte production observed in this group com-

pares favorably with that previously reported[2] in a group of patients treated with the 3 cc. material derived from comparable amounts of liver, that is, from 400 to 700 gm. during the first month. That the actual rate of erythrocyte production is slower in many of

TABLE 1.—DATA OBTAINED DURING THE FIRST 4 WEEKS OF TREATMENT OF 28 PATIENTS WITH INTRAMUSCULAR INJECTIONS OF A CONCENTRATED LIVER EXTRACT.

| Case No. | Peak of "retic" rise. % | Day of "retic" peak. | Initial R.B.C. level in millions per c.mm. | Daily R.B.C. increase in thousands during 4 weeks. | | | | Amount of extract injected, in cc.* | Day given. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 1st. | 2d. | 3d. | 4th. | | |
| 1 | 32.1 | 5 | 1.08 | 146 | 150 | ... | 116 | 4 | 0 |
| 2 | 23.1 | 4 | 1.13 | 63 | 108 | 68 | 65 | 4 | 0 |
| 3 | 34.1 | 5 | 1.15 | 130 | 123 | 99 | 83 | 1 | 0–12 |
| 4 | 21.0 | 5 | 1.27 | 104 | 160 | ... | 94 | 1 | 1–9–12 |
| | | | | | | | | | 15–21–23 |
| 5 | 18.6 | 5 | 1.58 | 90 | 102 | 90 | 88 | 2 | 0–1 |
| | | | | | | | | 1 | 25 |
| 6 | 16.2 | 4 | 1.60 | 83 | 96 | 105 | 99 | 2 | 0–1 |
| 7 | 28.8 | 6 | 1.67 | 230 | 116 | 133 | 108 | 2 | 0–1 |
| 8 | 30.2 | 4 | 1.67 | 83 | 106 | ... | ... | 1 | 0 |
| 9 | 17.7 | 5 | 1.79 | 97 | 103 | 85 | 75 | 1 | 0–19 |
| 10 | 10.2 | 6 | 2.02 | 72 | ... | ... | 85 | 1 | 0–10 |
| | | | | | | | | | 18–25 |
| 11 | 8.0 | 6 | 2.03 | 124 | 78 | 87 | 74 | 2 | 0 |
| | | | | | | | | 1 | 15 |
| 12 | .... | ... | 2.08 | 146 | 78 | 58 | 61 | 1 | 0–8–18 |
| 13 | .... | ... | 2.18 | 143 | ... | ... | 53 | 2 | 0–1 |
| | | | | | | | | 1 | 7–14–21 |
| 14 | 11.5 | 4 | 2.36 | ... | 108 | ... | ... | 4 | 0 |
| 15 | 21.9 | 7 | 2.36 | 146 | 110 | 96 | 81 | 2 | 0 |
| | | | | | | | | 1 | 7–14–21 |
| 16 | 4.7 | 6 | 2.43 | 67 | 70 | 70 | 77 | 1 | 0–10–18 |
| 17† | 24.6 | 9 | 2.04 | 64 | 69 | 87 | ... | 0.14 | Daily for 28 days |
| 18† | 13.1 | 6 | 2.46 | 66 | 97 | 71 | 73 | 0.1 | Daily for 28 days |
| 19 | 5.0 | 6 | 2.57 | ... | 51 | 39 | 40 | 1 | 0–6–13–20 |
| 20 | 7.6 | 6 | 2.63 | 76 | 116 | 120 | ... | 2 | 0–1 |
| | | | | | | | | 1 | 12 |
| 21 | 19.9 | 4 | 2.73 | 54 | 89 | 80 | 104 | 2 | 0–1 |
| 22 | 7.2 | 5 | 2.82 | 114 | 116 | ... | 63 | 1 | 0–18 |
| 23 | 7.8 | 5 | 2.84 | 107 | 96 | 96 | 63 | 2 | 0–1 |
| | | | | | | | | 1 | 7–14–21 |
| 24 | 10.4 | 5 | 3.00 | 113 | 105 | 73 | 75 | 2 | 0–1 |
| | | | | | | | | 1 | 7–14–21 |
| 25† | 13.5 | 7 | 2.69 | 0 | 43 | 28 | 55 | 0.1 | Daily for 28 days |
| 26 | ... | ... | 3.01 | 80 | 83 | 47 | 53 | 2 | 0–1 |
| | | | | | | | | 1 | 7–14–21 |
| 27 | 2.9 | 5 | 3.23 | 0 | 47 | 60 | 60 | 2 | 0–2 |
| | | | | | | | | 1 | 13 |
| 28 | 5.1 | 7 | 3.36 | 6 | 69 | 70 | 56 | 2 | 0–1 |
| | | | | | | | | 1 | 7–14–21 |

* 1 cc. = 1 vial derived from 100 gm. of liver (Lederle Laboratories, Inc.).
† Extract administered in small daily dosage for 28 days.

this group than the averages previously reported is no doubt due to the fact that they received, during the first 4 weeks, extract derived from smaller quantities of liver, that is, from 200 to 400 gm. However, the average daily erythrocyte increase during 28 days for the 9 patients whose initial erythrocyte levels were below 2,000,000 (see Table 1) was approximately 92,000, as compared with 98,000 per day for a similar group previously reported,[1,2] and treated with the 3 cc. material.

TABLE 2.—THE AGE, TIME ELAPSED AFTER ONSET OF TREATMENT FOR ERYTHROCYTE COUNTS TO REACH ABOUT 4,500,000 AND 5,000,000 LEVELS AND THE AMOUNTS OF LIVER EXTRACT USED IN THE 28 PATIENTS OF TABLE 1.

| Case No. | Age. | Weeks to 4.5+ m. | Weeks to 5.0+ m. | Total No. of injections. | Total amount of liver, gm.* |
|---|---|---|---|---|---|
| 1 | 27 | 5 (4.55) | 6 (5.19) | 6 | 600 |
| 2 | 60 | 6 (4.71) | 11 (5.37) | 8 | 800 |
| 3 | 68 | 6 (4.85) | 8 (5.88) | 6 | 600 |
| 4 | 71 | 6 (4.72) | 8 (5.03) | 10 | 1000 |
| 5 | 63 | 6 (4.63) | 8 (5.49) | 9 | 900 |
| 6 | 61 | 5 (4.69) | 9 (5.08) | 10 | 1000 |
| 7 | 57 | 3 (4.57) | 5 (5.55) | 7 | 700 |
| 8 | 68 | | | | |
| 9 | 63 | 8 (4.83) | 13 (5.08) | 10 | 1000 |
| 10 | 69 | 7 (4.41) | 20 (5.80) | 15 | 1500 |
| 11 | 65 | 6 (4.75) | 7 (5.60) | 4 | 400 |
| 12 | 61 | 8 (4.69) | 17 (5.39) | 8 | 800 |
| 13 | 42 | 7 (4.69) | 16 (5.25) | 13 | 1300 |
| 14 | 46 | 7 (4.82) | 11 (5.78) | 11 | 1100 |
| 15 | 55 | 4 (4.63) | 5 (5.60) | 6 | 600 |
| 16 | 70 | 10 (4.83) | 20 (5.19) | 12 | 1200 |
| 17 | 65 | 5 (4.96) | 7 (5.52) | 5 | 500 |
| 18 | 58 | 4 (4.49) | | | |
| 19 | 61 | 8 (4.55) | | | |
| 20 | 47 | 3 (5.14) | 3 (5.14) | 5 | 500 |
| 21 | 41 | 4 (5.65) | 4 (5.65) | 7 | 700 |
| 22 | 54 | 4 (4.46) | 8 (5.16) | 5 | 500 |
| 23 | 52 | 3 (4.85) | 5 (5.61) | 8 | 800 |
| 24 | 45 | 3 (4.53) | 4 (5.11) | 7 | 700 |
| 25 | 77 | 9 (5.36) | 9 (5.36) | 6 | 600 |
| 26 | 64 | 4 (4.48) | 16 (5.18) | 10 | 1000 |
| 27 | 64 | 3 (4.48) | 5 (5.03) | 7 | 700 |
| 28 | 75 | 3 (4.81) | 6 (5.09) | 9 | 900 |

* The figures in this column indicate the total amount of liver from which the extract was prepared that was administered from the beginning of treatment during relapse to the time that the erythrocyte level reached 5,000,000 or more.

Erythrocyte counts were made at the end of 4 weeks on 24 of the patients. In 17 instances the level had reached 4,000,000 or more and in only 1 instance was the level below 3,500,000 at this interval. In 19 instances a level of 4,500,000 had been reached within 6 weeks of the onset of treatment and within 8 weeks after treatment was begun the erythrocyte level was over 5,000,000 in 15 instances, as shown in Table 2. Failure of the blood to reach 5,000,000 or more within about 8 weeks or less (Table 2) was usually due either to failure on the part of the patient to appear regularly for treatment or for blood counts at the proper intervals. The

amount of material used before reaching this level averaged approximately 1 cc. prepared from 100 gm. of liver each week.

Ten of the patients (Cases 10, 12, 13, 14, 15, 19, 21, 23, 24 and 26) received their initial treatment as ambulatory patients and in most instances continued at their usual occupations. This has apparently made little difference in the rate of improvement in most instances. Three cases, however, warrant special comment.

The patient shown as Case 10 has been under treatment with rather large amounts of whole liver, peroral liver extract or ventriculin since June 10, 1927. During this time and until the intramuscular injections were started she has remained in a fair state of health but with an average erythrocyte count of only 4,000,000. The maximum level reached at any time was 4,800,000. She states that since starting the 1 cc. injections on July 16, 1935, she has felt better than at any time during her illness, and the extreme hyperesthesia of the hands and fingers, which made life miserable for her, has practically disappeared for the first time. The erythrocyte count has averaged above 4,500,000 since 6 weeks after treatment was started and has averaged above 5,000,000 for 2 months, while receiving an injection of 1 cc. at 8-day intervals.

Case 19 began treatment for the first time on January 24, 1935, as an ambulatory patient. She has continued at unusually hard work as a housekeeper throughout her entire period of treatment and without adequate rest. It is a well-known fact that rest favors the production of erythrocytes, whereas fatigue acts to slow-up their production. This patient has required unusually large amounts of material during a period of nearly a year in order to maintain her blood in a fairly satisfactory state (an average of about 4,500,000). Data concerning maintenance treatment is not contained in Table 3 because her treatment was changed to injections of 3 cc. material during that time.

One other patient (Case 13) deserves special comment. During her early treatment as herein recorded she developed an acute attack of appendicitis, was operated upon and in spite of this reached a level of over 5,000,000 in 16 weeks. Except during her period of hospitalization for the operation she continued with her duties as a housewife, caring for several children.

**Maintenance Requirements.** Perhaps the most critical and important means of evaluating the efficiency of the various substitutes for liver is the determination of the amount of the antianemic material that is necessary in order to maintain the erythrocyte count at a normal level. In order that this procedure may be of distinct value the interval of maintenance observation should as stated, cover a period of time of not less than 6 months, and longer intervals are preferable.

The data obtained in connection with the maintenance treatment of 21 patients by means of intramuscular injections of the 1 cc. extract are shown in Tables 3 and 4.

TABLE 3.—DURATION OF MAINTENANCE TREATMENT, INTERVAL BETWEEN INJECTIONS OF 1 CC. OF LIVER EXTRACT DERIVED FROM 100 GM. OF LIVER AND THE AVERAGE ERYTHROCYTE COUNTS DURING THE ENTIRE PERIOD OF OBSERVATION FOR 16 OF THE CASES OF TABLE 1.

| Case No. | Duration of maintenance, weeks. | Average interval between injections, days. | Average R.B.C. count, millions. |
|---|---|---|---|
| 4 | 33 | 10 | 5.00 |
| 6 | 37 | 16 | 4.97 |
| 3 | 24 | 17 | 4.86 |
| 5 | 36 | 17 | 4.80 |
| 12 | 25 | 18 | 4.87 |
| 28 | 53 | 19 | 5.26 |
| 2 | 30 | 21 | 5.34 |
| 7 | 39 | 21 | 5.64 |
| 22 | 28 | 22 | 4.92 |
| 24 | 39 | 23 | 5.65 |
| 11 | 52 | 23 | 5.83 |
| 1 | 34 | 24 | 5.41 |
| 17 | 32 | 25 | 5.57 |
| 23 | 44 | 26 | 5.26 |
| 27 | 48 | 26 | 5.35 |
| 25 | 27 | 28 | 5.45 |

In Table 3 are presented the data obtained in 16 of the 28 patients, first treated during relapse who have been observed for from about ½ to 1 year after the erythrocyte level had reached 4,500,000 or more.

The results shown compare favorably with data previously obtained[4] with treatment by means of intramuscular injections of 3 cc. of liver extract derived from 100 gm. of liver (Lederle) in a series of 89 patients treated for intervals varying from ½ to 2½ years. In this group the average interval between injections of one vial or 3 cc. was approximately 4 weeks, whereas in the group of patients whose data is recorded in Table 3 the average interval between injections of 1 vial or 1 cc. is approximately 3 weeks. A larger series of cases observed over a longer interval of time might easily favorably influence this interval.

TABLE 4.—COMPARISON BETWEEN THE DURATION OF MAINTENANCE TREATMENT, INTERVAL BETWEEN INJECTIONS OF 1 AND 3 CC. OF LIVER EXTRACT DERIVED FROM 100 GM. OF LIVER AND THE AVERAGE ERYTHROCYTE COUNTS DURING THE ENTIRE PERIOD OF OBSERVATION FOR 5 PATIENTS.

| Case No. | Initial R.B.C. count, millions. | Duration of maintenance, weeks. | Average interval between injections, days. | Average R.B.C. count, millions. | No. of injections. | Amount each injection, in cc.* |
|---|---|---|---|---|---|---|
| 29 | 4.68 | 48 | 17 | 4.40 | 20 | 3 |
| | 4.45 | 57 | 15 | 4.65 | 27 | 1 |
| 30 | 4.68 | 59 | 16 | 4.97 | 24 | 3 |
| | 5.19 | 59 | 13 | 4.74 | 31 | 1 |
| 31 | 4.82 | 97 | 14 | 4.85 | 48 | 3 |
| | 4.19 | 55 | 19 | 5.04 | 20 | 1 |
| 32 | 5.24 | 83 | 28 | 5.19 | 21 | 3 |
| | 5.19 | 57 | 25 | 5.19 | 16 | 1 |
| 33 | 4.61 | 105 | 23 | 5.23 | 31 | 3 |
| | 5.05 | 58 | 18 | 5.29 | 23 | 1 |

* Each injection of 1 or 3 cc. represents 1 vial prepared from 100 gm. of liver (Lederle Laboratories, Inc.).

Further evidence of the similarity of the efficiency of these two concentrated and highly potent extracts is shown in Table 4. It is to be remembered that these patients were chosen as test subjects for the 1 cc. extract because they had been found to require somewhat more of the 3 cc. material than the average of the group treated, as described in the preceding paragraph. The interval between injections is essentially the same with the use of either extract and the average interval of 19 days for the entire period on the two extracts is similar to the average interval between injections of 1 cc. as shown in Table 3.

In the 21 cases reported in Tables 3 and 4 erythrocyte counts have been made on essentially each return visit of the patient for injection. An occasional count has been missed through unavoidable circumstances. It has been our aim, as in previously reported data,[3,4,5] to maintain the erythrocyte level at or above 5,000,000 cells per c.mm., for the cells are usually found to remain normal in all demonstrable respects under those circumstances. Only rarely, in this reported group, have we failed to maintain such an average and this failure has usually been dependent upon a temporary drop in the count caused by an intercurrent infection or complication which has not been taken into account in this discussion in the interest of brevity.

**Discussion.** The advantages, to both the patient with pernicious anemia and his physician, of the use of a highly concentrated liver extract for intramuscular injection in which a high degree of potency has been retained, so that relatively small dosage is needed during relapse in order to produce prompt and striking increases in the number of erythrocytes and which need be administered only infrequently in order to maintain a normal state of the blood over an extract for peroral use necessary in large daily dosage and particularly over the use of extracts of low concentration or potency for parenteral use, are obvious. These advantages have been previously stated so need no further discussion here.[6–11]

The data presented herein demonstrate the high degree of efficiency of this newest and most highly concentrated liver extract which has been developed on a commercial scale for parenteral use. The evidence is in part based upon a comparison with a concentrated extract previously demonstrated to retain a high degree of potency.[3,4] The comparison is made primarily upon the basis of the value of the extract in producing erythrocytes in patients treated during relapse and upon its efficiency in maintaining a normal state of the erythrocytes during intervals of time varying from about 6 to slightly more than 12 months.

Little attention has been paid to the reticulocyte rise as an indication of the effectiveness of this material, for this phenomenon has little value in determining the comparative efficiency of extracts. Observation only of the magnitude of the reticulocyte rise gives

merely an indication of the presence of potency, but not of its degree of potency.[2] The aim of treatment of the patient with pernicious anemia is to produce as quickly as possible a normal erythrocyte count and to maintain a normal state of the blood and the best state of health possible for each patient.[5] The most efficient means of doing this is to use that form of therapy which will accomplish the desired end with the least expense and inconvenience for the patient. Consequently any determination of potency which will be of practical value to the physician in demonstrating what extract is best to use because of its efficiency must be based on its ability to produce erythrocytes and to maintain the blood in a normal state (5,000,000 erythrocytes per c.mm. of blood) in a fairly large group of cases treated with a more or less uniform dosage. This has been done in the treatment of the patients as herein reported.

Although satisfactory erythrocyte increases have been produced during a period of 4 weeks with the use of as little as two vials (2 cc. prepared from 200 gm. of liver) and the average maintenance dose has been as little as one vial (1 cc. prepared from 100 gm. of liver) given at intervals of about 21 days, this has not been true of all patients. Consequently, and because it is best to give maximum rather than minimum amounts for the patient's best interest, one should give injections of more material than that shown as the average unless the erythrocyte level may be checked accurately and at rather frequently intervals so that the dose may be varied as may be indicated by the condition found.

With the use of less concentrated and less potent material it is obvious that injections must be given more frequently and in larger quantity. Although such an extract has obvious disadvantages, for both physician and patient, particularly as to technique of administration and discomfort to the patient, a less obvious but important disadvantage to the patient is that of the expense. One cannot substitute one extract for another, vial for vial or quantitatively, any more than different preparations of digitalis, thyroid substance or vitamins are so interchangeable, for the concentration and potencies vary. Until a system is available whereby the potency may be expressed in units, the safest means of assuring the patient of the best material is on the basis of the amount of potent material, efficient in erythrocyte production, which is present in extract derived from a known quantity of liver.

The material used in this study (1 cc. derived from 100 gm. of liver) has been demonstrated to be essentially equivalent to an extract previously shown to contain a high degree of efficiency; that is, 3 cc. derived from 100 gm. of liver was found to have the erythrocyte-producing or maintenance potency of 30 to 50 or more times that of the amount of liver from which it is prepared, if that liver were given by mouth.[6,7] The high degree of potency of the

3 cc. extract has been confirmed, on the basis of the demonstration of its erythrocyte-producing effect during relapse by Connery and Goldwater,[12] and by Alt,[13] and Connery and Goldwater,[14] by determination of the maintenance requirements during periods of 6 months or more. In both studies the average interval between injections of 3 cc. material derived from 100 gm. of liver was 2 to 3 weeks in order to maintain the erythrocyte levels at or near 5,000,000 per c.mm. of blood.

The degree of potency retained in the extract used in the treatment of the patients reported herein is further demonstrated by a comparison of its effect with that of other liver extracts which have been tested for erythrocyte-producing effect and for maintenance requirement. The methods of recording data varies so much in the reports that no attempt will be made to analyze them in detail, but for further information the reader is referred to the original articles. Unfortunately few reports are available concerning the maintenance requirements of other extracts which include a sufficiently long period of observation or number of patients to give a satisfactory indication of the value of the extract. In analyzing data of this sort one must also bear in mind the importance of the erythrocyte levels which are maintained, for it takes an appreciably greater amount of material to maintain the levels at 5,000,000 or higher than it does to maintain them at lower levels.

Zerfas[15] observed the erythrocyte increases during a period of 1 month in 61 patients treated during relapse with the daily ingestion of extract prepared from 300 to 1000 gm. of liver. The erythrocyte count reached 4,000,000 or more during this interval in only 5 patients. Fouts and Zerfas[16] report the maintenance of "normal" erythrocyte levels in 38 patients during an average period of 3 years with extract derived from 300 gm. or less (average, 223 gm.) of liver, whereas the levels in 21 patients were not maintained with an average daily ingestion of extract derived from 381 gm. of liver. Isaacs, Sturgis, Goldhamer and Bethel[17] found that in 8 patients with an average erythrocyte level of 840,000 it required 63.9 days to reach an average count of 4,350,000 with an average gain of 56,000 cells per day during this period, using intravenous injections of extract, probably 20 cc. prepared from 100 gm. of liver, at weekly intervals. The exact dosage is not stated. In 10 patients, similarly treated, with an average initial level of 1,420,000 it required 50 days to reach an average level of 4,290,000. The average daily gain during the entire period was 61,000. In a third group of 21 patients with an average initial count of 2,630,000 it took 42.9 days to reach an average of 4,380,000. They further report an average daily gain of 98,000 for the first 2 weeks of treatment in the first group and of 82,000 in the second group. This is to be compared to average increases of 137,000 and 105,000, respectively, in two groups with comparable initial levels and treated with the 1 cc.

material as recorded in Table 1. Isaacs and his co-workers maintained "normal" erythrocyte levels in 56 patients during a period of from 6 to 17 months with intravenous injections of 20 cc. of extract once each month. Meyer, Richter and Ivy[18] observed average daily gains of 59,000 erythrocytes in 13 patients treated with an average daily subcutaneous or intravenous injection of 1.6 cc. of equine liver extract for periods of from 9 to 73 days. They report that each 1 cc. is "equivalent" to 10 gm. of liver. Meyer, Richter and Legere[19] report the results of treatment of 6 patients with subcutaneous injections of extracts prepared from pre-digested equine liver (with stomach mucosa). Injections representing the extract from 475 to 1825 gm. of liver were given during periods of from 16 to 73 days with an approximately similar daily gain. They conclude that this material has slightly greater potency than was present in their equine liver extract. It is difficult to use their data for the purposes of comparison because of the varied periods of treatment, but the indications are that the material is of relatively low potency as compared to the material herein considered. Bethel[20] has reported the length of time necessary to bring the erythrocytes to a level of 4,000,000 in 150 cases treated with weekly intramuscular or intravenous injections of 10 to 20 cc. (prepared from 50 to 100 gm. of liver). In those patients with initial erythrocyte counts below 2,500,000 it took 5 weeks, whereas it took only 4 weeks in those with initial counts between 2,500,000 and 3,000,000 and lesser periods of time in those with higher initial counts.

**Conclusions.** The material used in the treatment of the patients under consideration in this study has an antianemic effectiveness for erythrocyte production during relapse of from 20 to 40 times the amount of liver from which it is prepared and for maintenance purposes from 50 to 70 times the amount of liver from which it is prepared if that were ingested. It is also apparent that this extract for intramuscular injection so prepared that 1 cc. is derived from 100 gm. of liver has retained the antianemic potency to an extent entirely comparable to that retained in the most efficient of those less highly concentrated extracts for parenteral use upon which satisfactory potency tests have been carried out.

Therefore, because of its high degree of efficiency, ease of administration and reasonableness of cost, in consideration of its effectiveness, this extract is the ideal one for use.

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## EXPERIMENTAL RADIUM POISONING.

### I. Bone Marrow and Lymph-node Changes in Rabbits, Produced by Oral Administration of Radium Sulphate.*

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Although the intravenous administration of radium salts in the treatment of sundry ailments has in a few instances resulted in radium poisoning, the great majority of human cases have been

* This investigation has been made with the assistance of a grant from the Committee on Therapeutic Research, Council on Pharmacology and Chemistry, American Medical Association.

brought about by ingestion or inhalation of radio-active substances, the victims being chiefly watch-dial painters, chemists, miners and consumers of radium-water nostrums. Nevertheless in none of the experimental studies of this condition have radio-active materials been administered orally. This fact is of interest, for, as will be seen, certain discrepancies exist between the lesions that have been found in experimental animals and those in the humans.

Lacassagne and his coworkers,[1] in 1925, reported the production of acute and chronic forms of nephritis together with marked changes in the blood-forming centers by the intravenous and intraperitoneal injection into rabbits of lethal doses of polonium, a decay product of radium emitting only alpha rays. Within 5 days the bone marrow showed an almost complete loss of erythrocytic and leukocytic elements and presented the histologic picture of an acellular fatty marrow. Sabin and her co-workers,[2] in 1932, studying the effects of the intravenous injection of radium chlorid and mesothorium on the lymph nodes and bone marrow of rabbits, found that the fundamental damage was in the stem cells of the lymphoid tissues. They could find no significant changes in the granulocytic cells of the marrow. They concluded that the erythroid tissues are less susceptible to radio-active material than the lymphoid tissues, although they observed that an early mild anemia of secondary type, developing from peripheral destruction, might eventually be changed to one of primary type through a decreased maturation of primitive cells in the marrow. Two of the 7 rabbits in their series, surviving 11 and 19 months respectively, developed osteogenic sarcomata due apparently to storage of radio-active material in the bone. Thomas and Bruner[3] in 1933 made a study of chronic radium poisoning in rats, produced by subcutaneous injection of radium chlorid. In a series of 8 albino rats, these authors reported the occurrence of marked loss of weight, pathologic fractures, secondary anemia, hyperplasia of the marrow in the central two-thirds of the shafts of the long bones, and aplasia of the marrow of the flat bones. The hyperplastic changes in the marrow consisted of an increase in the myelocytic cells with an abundance of megakaryocytes. They also noted damage to the lymphoid tissues and parenchymatous organs. Foci of extramedullary myelopoiesis were found in the spleen, lymph nodes and liver.

De Laet,[4] in his general review on the deleterious effects in humans from the handling of radio-active substances and exposure to Roentgen rays, cites the occurrence of the following blood dyscrasias; aplastic anemias, leukopenias, leukemias (myelogenous and lymphatic) and occasionally primary anemias. Most of the cases reviewed had not been autopsied nor had studies of the bone marrow been made to determine the exact types of blood dyscrasia. In Martland's[5] observations on victims of radium poisoning by ingestion and inhal-

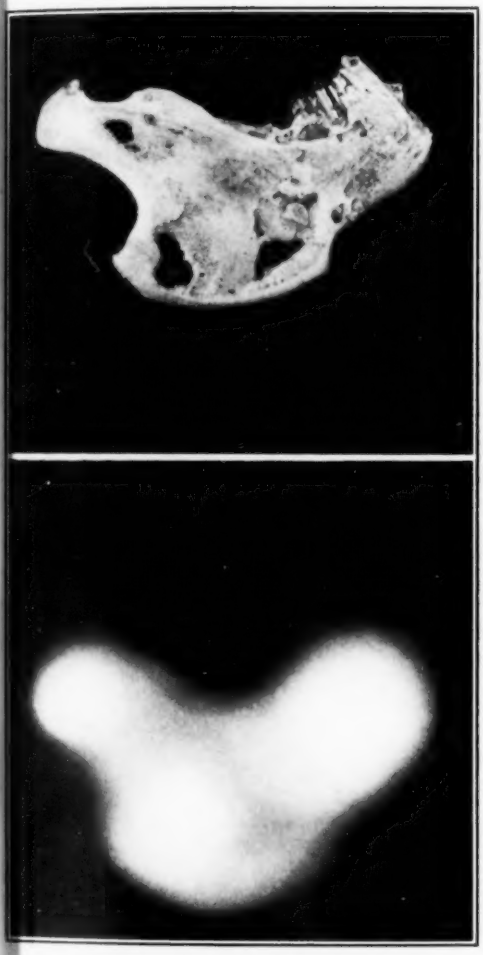


FIG. 1

FIG. 3

FIG. 1.—*Above.* Mandible showing osteoporosis and large fenestrations in mandibular plate. Due to fragility of bone the mental process with incisor tooth was separated in preparation. *Below.* Autophotograph of the same mandible indicating presence of radium in bone.

FIG. 3.—Autophotograph of femur of Rabbit 4 showing patchy distribution of radium as the result of bone destruction and reconstruction in a later stage of radium poisoning. This bone was not the seat of a fracture, although the peculiar radium distribution might suggest fracture of the shaft.

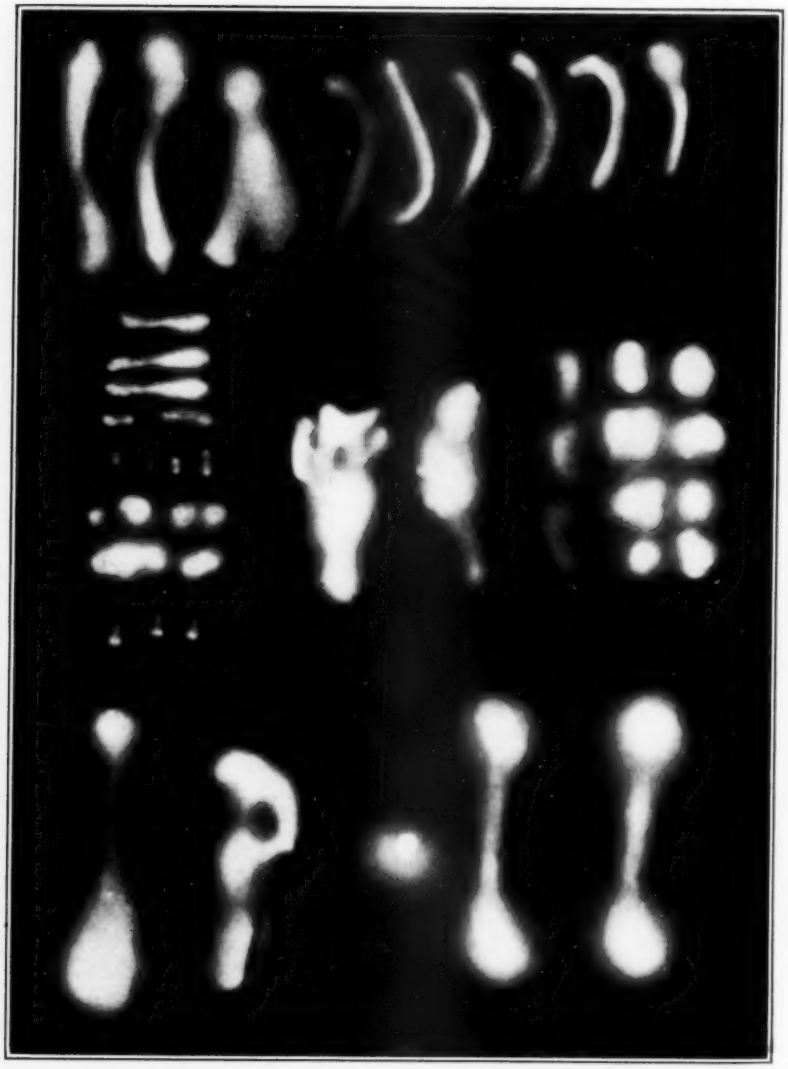


FIG. 2.—Autophotograph of various bones of Rabbit 1 showing more or less uniform distribution of radium in an early stage of radium poisoning.

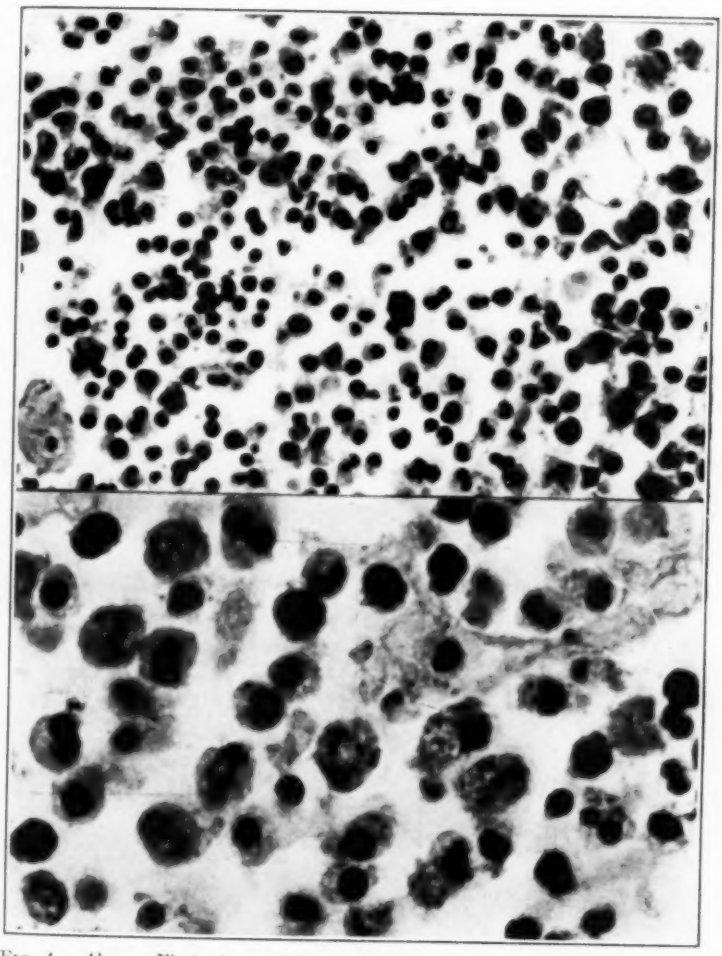


FIG. 4.—*Above.* First stage of hyperplastic marrow, the predominating cells being of the erythroblastic series. *Below.* High power of above shows the majority of the cells to be erythroblasts and normoblasts.

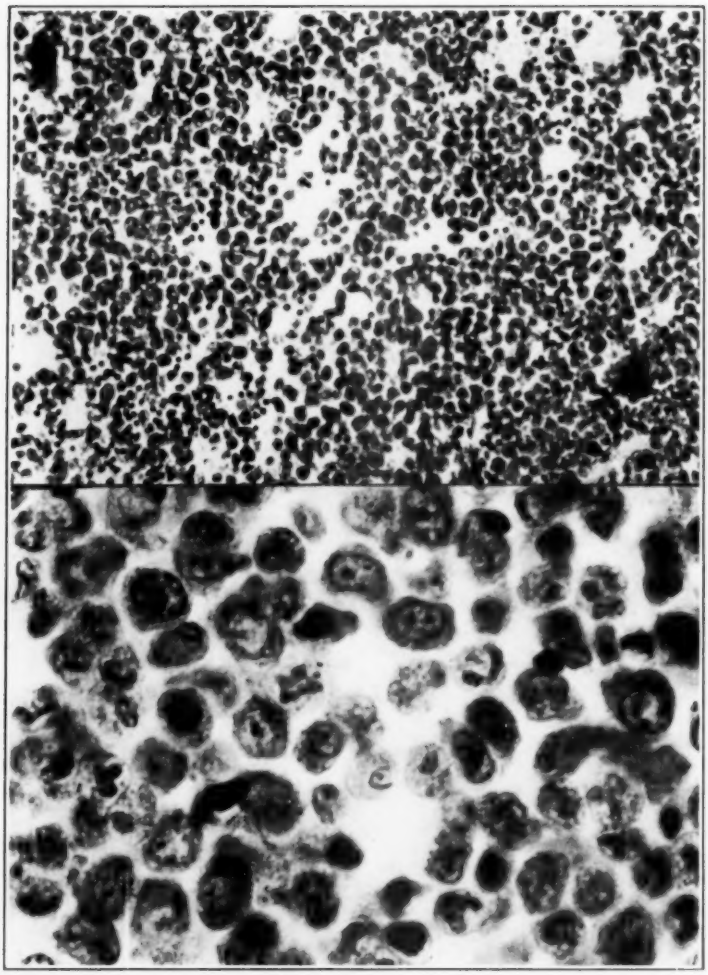


FIG. 5.—*Above.* Marked hyperplasia of marrow at midfemur, the predominant cells being myelocytes among which a few clumps of erythroblasts and normoblasts may be seen. *Below.* High power of above showing the majority of the cells to be myelocytes with a few late erythroblasts and normoblasts.

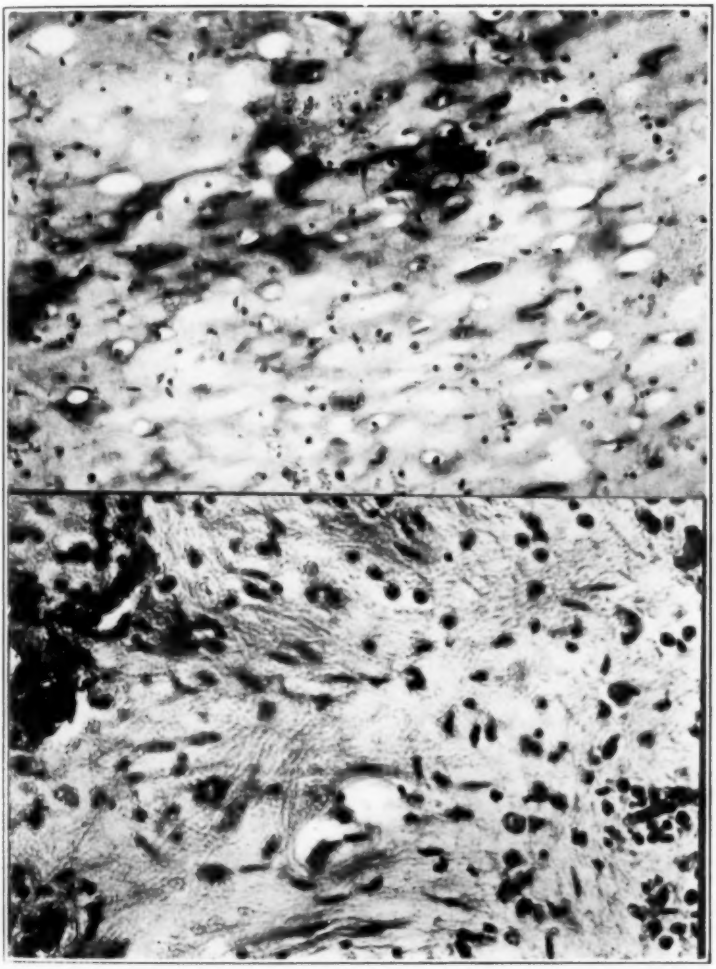


FIG. 6.—*Above.* Mucoid degeneration of marrow: the strands of large dark cells are degenerating reticulum cells. *Below.* Fibroblastic replacement of degenerating marrow.

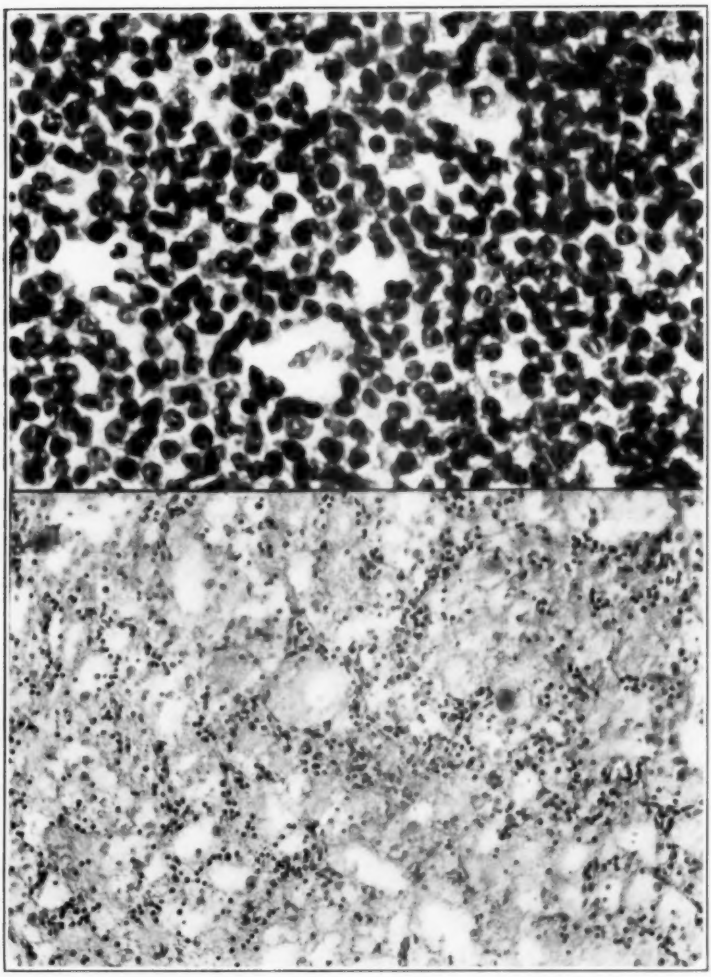


FIG. 7.—*Above.* Markedly hyperplastic area of lymph node, the predominant cells being lymphoblasts among which are a few mature lymphocytes and degenerating stem cells. *Below.* Marked cellular depletion of lymph node: the faint outlines of degenerating stem cells in a background of cell débris can be seen.

ation there were found at autopsy leukopenic anemias of the regenerative type and marked changes in the marrow.

In the light of the disagreement between the various experimental findings and the findings in the human cases there still would seem to be some doubt as to the exact nature of the anemias and the lymph gland and marrow changes. We have thought therefore that study of the bone marrow and other tissues from animals that had been given radium salts *per os* might help to explain the pathogenesis of these blood tissue alterations.

**Material and Methods.** Four rabbits 6 months of age were used, of which 2 were males, each weighing 2700 gm., and 2 females, each weighing 1800 gm. The animals were kept on a normal and adequate standard diet throughout the experiment. Each animal was fed several drops of a suspension of radium sulphate in glycerin by a medicine dropper 3 times daily for a period of 90 consecutive days. By the end of this period each rabbit had received orally approximately 100 micrograms of radium sulphate. Glycerin was found to be a suitable vehicle and the animals seemed to enjoy the sweet taste, thus assuring ingestion of most of the radium salts. The rabbits were observed daily for physical changes, and blood studies were made bi-weekly. The animals survived for 3, 12, 13 and 18 months, respectively, after the cessation of radium administration.

In studying the marrow of our rabbits we employed the procedure recommended by Krumbhaar and Custer.[9] These authors recommend making differential counts of marrow sections, a procedure which gives accurate information concerning the status of the hemopoietic tissue.

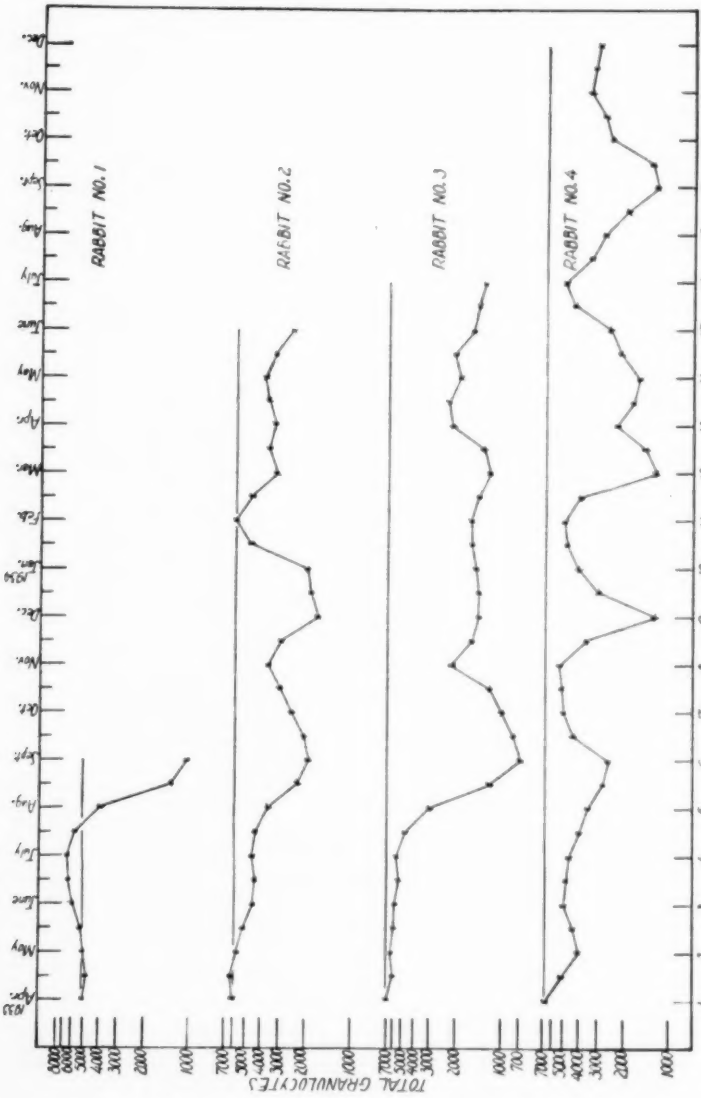
*Physical Changes During Life.* For the first 2 months of the radium administration the animals showed no abnormal changes. During the third month, however, the lower incisor teeth of all showed a brown mottling. In the next few weeks this mottling became more marked and the teeth were observed to be definitely shortened. Associated with these dental changes was a gingivitis, and in manipulating the jaws during the administration of the radium there was manifested a progressive tenderness.

One month after cessation of radium administration a diffuse thinning of the fur occurred in all the animals and a month later definite local areas of alopecia were observed in the peri-orbital regions and over the hind legs. No further physical changes were noted until 3 months after cessation of radium administration when Rabbit 1 developed a spontaneous fracture of the third lumbar vertebra associated with a flaccid paralysis of the hind legs. Two days later the animal died. The necropsy findings will be discussed later.

During the following 6 months the lower incisor teeth of the remaining rabbits became shortened to about 2 mm. above the gum margins. The upper incisors showed to a lesser degree the same changes, the sharp incisive edges being worn off (abraded) with the formation of broad occluding surfaces. In the meantime these animals developed abscesses of the jaw and Roentgen ray examination revealed irregular areas of rarefaction of the mandibular plates. The abscesses subsided spontaneously. By this time (9 months after cessation of radium administration) Rabbits 2, 3 and 4 had lost 350, 250 and 100 gm. respectively in weight. Five weeks later Rabbit 3 developed spontaneous fractures of both femora and tibiæ and lived 7 weeks longer without developing any further visible complications. In the meantime Rabbit 2 developed multiple fractures of both hind legs and died the following day, 12 months after the end of treatment.

Thirteen months after the end of radium administration the only surviving rabbit (No. 4) developed an abscess of the jaw which perforated

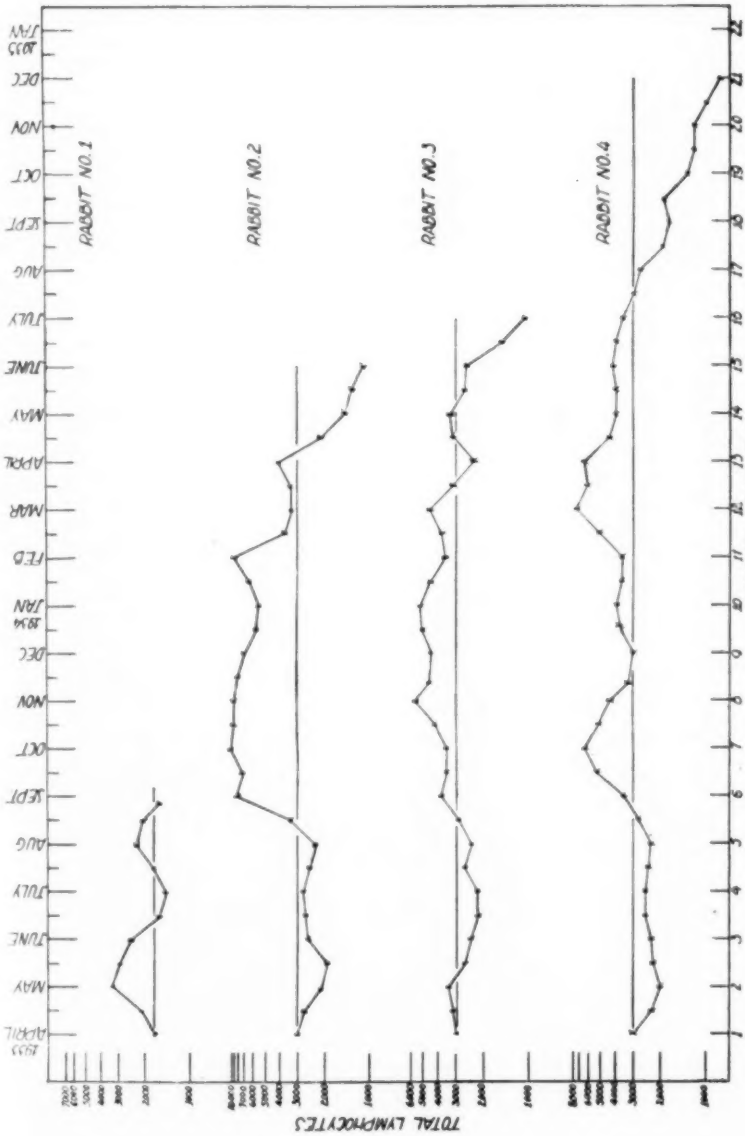
and drained into the buccal cavity. Roentgen ray studies at this time revealed large irregular areas of rarefaction in the right mandibular plate. Aside from the fact that the lower incisors were worn down to the gum margin, this animal showed no physical changes until one day before death




GRAPH 1.—Representation in absolute figures of the lymphocyte counts, throughout the survival period of each animal.

when it developed a spontaneous fracture of the lower lumbar vertebra with an associated flaccid paralysis of both hind legs. The following day (18 months after radium administration) the rabbit was killed by intravenous injection of air.

*Changes in the Circulating Blood.* With the exception of one animal (Rabbit 1) that lived only 3 months after treatment, all showed mild pro-




GRAPH 2.—Representation in absolute figures of the granulocyte counts throughout the survival period of each animal.

gressive anemia with slight remissions. There was a gradual decrease in hemoglobin in all of the animals and the color index, despite slight fluctuations, showed a progressive fall. The blood smears showed signs of erythro-

cytic activity by an increase in the number of reticulocytes and the appearance of nucleated red cells. There was a moderate degree of poikilocytosis and anisocytosis. In a similar manner, despite occasional remissions, all of the animals (except Rabbit 1) showed a progressive fall in the total number of leukocytes. However, the differential counts revealed a prolonged period in which there were relative and absolute increases in lymphocytes, though these were not always concomitant (Graphs 1 and 2). These periods bore no relationship to the total number of leukocytes. In one animal (Rabbit 2) there was a marked terminal leukopenia.

Six months after radium administration various evidences of degeneration were seen in the granulocytes and lymphocytes. In the former the cell membrane very rarely remained intact in the blood smears, the cytoplasmic granules being intercellularly dispersed. The nuclei stained poorly and the nuclear membrane was indistinct. Occasionally the nuclei were found to be extruded. The lymphocytes stained poorly and showed fragmentation of the nuclei.

*Necropsy Findings.* Rabbits 1 and 4 that developed spontaneous fractures of the lower lumbar vertebræ with cord compression showed retroperitoneal hemorrhages which had infiltrated the psoas muscles. In Rabbits 2 and 3 there were hemorrhages into the soft tissues overlying the fractures of the long bones.

The lymph nodes and spleens of Rabbits 2, 3 and 4 were generally decreased in size. No other gross changes were observed in the thoracic, abdominal and pelvic organs.

In all of the rabbits the long bones, especially the femora and tibiæ, showed, in addition to the fractures described above, a thinning and porous condition of the compact bone. There was also marked thinning of the cortex of the flat bones and in some of these the red marrow could be easily seen through the thin cortex. The most striking pathologic changes, however, were found in the mandibles where the mandibular plates were extremely thinned and in several instances fenestrated (Fig. 1). All of the bones were very fragile. Though no macroscopic tumors of the bones were noted, in Rabbit 3 there were numerous nodular bony enlargements measuring 4 to 6 mm. in size in many of the ribs. None of these nodules occurred at the costochondral junctions.

The marrow of the long bones, ribs and vertebræ was of the red variety in all of the animals except Rabbit 4 where it was pinkish-gray in color. Near the epiphyseal ends of the femora of this animal a few grayish-white areas 2 to 3 mm. in size were seen.

*Microscopic Findings.* The most important histologic changes were found in the bones, teeth and hemopoietic organs.

The osseous system, especially the femora, tibiæ, ribs, vertebræ and mandibles, showed a marked generalized osteoporosis and most of the compact bone was necrotic. There was atrophy of the trabeculæ in the epiphyseal ends of the long bones and widespread subendosteal and subperiosteal cortical resorption. Numerous Howship's lacunæ were seen with only occasional osteoclasts. The Haversian canals were enlarged and their walls were also irregularly indented by Howship's lacunæ. There were extensive foci of new bone deposition beneath periosteum and endosteum which bore no definite relationship to the sites of the fractures. Much of this new bone was also necrotic. The articular cartilages were extremely irregular in thickness due to marked focal hyperplasia interrupted by areas of necrosis. The nodules on the ribs of Rabbit 3, mentioned above, presented the appearance of bony calluses of healing fractures. The granulation tissue of the callus was exceedingly rich in blood capillaries and numerous giant cells with multiple nuclei were encountered in certain areas. The fibroblastic cells of this granulation tissue were particularly

large, showed immaturity approaching a definite anaplasia and presented many mitotic figures.

*Bone Marrow.* The general architecture of the marrow in all 4 rabbits was greatly altered. From the marrow of the middle third of the femur a differential cell count was made on each animal and compared with those of normal animals (Table 1).

On analysis of these counts it is found that Rabbit 1 showed a slight hyperactivity of the erythrocytic elements, the reaction being of normoblastic type with slight increase in erythroblasts. The eosinophilic myelocytes were within normal limits. The usual degenerative-regenerative balance of megakaryocytes was noted. In Rabbit 2, where erythropoietic islands were seen to be larger and more numerous than in the former animal, the increased erythropoiesis was of the normoblastic type though showing slight erythroblastic activity (Fig. 4). A moderate proliferative activity of myeloblasts was noted. There was a definite increase in eosinophilic myelocytes. The megakaryocytes were decreased slightly and showed a slight increase in the various degenerative forms.

TABLE 1.—DIFFERENTIAL COUNTS ON BONE MARROW, EXPRESSED IN PERCENTAGE (EACH COUNT BASED ON 1000 CELLS).

| | Control. | No. 1. | No. 2. | No. 3. | No. 4. |
|---|---|---|---|---|---|
| Granulocyte Series: | | | | | |
| Myeloblasts | 0.4 | 0.6 | 2.4 | 3.0 | 6.6 |
| Promyelocytes | 1.3 | 0.8 | 1.6 | 0.2 | 1.6 |
| Myelocytes: | | | | | |
| Neutrophils | 63.4 | 55.6 | 34.9 | 69.2 | 54.8 |
| Eosinophils | 1.4 | 1.6 | 3.3 | 4.0 | 8.4 |
| Basophils | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Metamyelocytes | 1.3 | 0.2 | 0.3 | 7.6 | 11.0 |
| Segmenters (all types) | 2.2 | 0.6 | 0.4 | 2.2 | 0.8 |
| | 70.00 | 59.4 | 42.9 | 86.2 | 83.2 |
| Erythrocyte Series: | | | | | |
| Erythroblasts | 3.7 | 6.8 | 6.0 | 8.1 | 11.0 |
| Normoblasts | 24.1 | 30.2 | 49.1 | 5.0 | 5.0 |
| | 27.8 | 37.00 | 55.1 | 13.1 | 16.0 |
| Thrombocyte Series: | | | | | |
| Megakaryocytes | 0.5 | 0.4 | 0.3 | 0.2 | 0.2 |
| Megakaryoblasts | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| | 0.5 | 0.4 | 0.3 | 0.2 | 0.2 |
| Reticulo-endothelial Series: | | | | | |
| Reticular cells | 1.0 | 2.0 | 1.2 | 0.2 | 0.2 |
| Endothelial cells | 0.2 | 0.4 | 0.3 | 0.2 | 0.2 |
| | 1.2 | 2.4 | 1.5 | 0.4 | 0.4 |
| Lymphocytic Series: | | | | | |
| Lymphocytes | 0.5 | 0.8 | 0.2 | 0.1 | 0.2 |
| Plasmacytes | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| | 0.5 | 0.8 | 0.2 | 0.1 | 0.2 |

The marrow changes of Rabbits 3 and 4 were more striking than those just described. In both of these animals there was a marked activity in the cells of the granulocytic series with a moderate increase in myeloblasts. However, the predominating cells were myelocytes and many of these

showed mitotic figures. A few scattered mature granulocytes were also found. The increase in myelocytes at the expense of the other marrow elements is suggestive of a so-called "replacement anemia" (Fig. 5). It is also interesting to note that although there was a marked decrease in erythropoietic cells, there was a relative increase in erythroblasts apparently the result of decreased maturation of these primitive cells. The eosinophilic myelocytes were increased, being most marked in Rabbit 4. These at times appeared in small groups or islands. The megakaryocytes were slightly decreased in number but showed an increase in the degenerative forms.

These cellular changes produced striking alterations in the topography of the bone-marrow sections. The proliferating myelocytes occurred in elongated islands many of which coalesced to form broad sheets. Occasional small clusters of erythroblastic cells were scattered throughout the myelocytic masses. Although most of the myelocytes appeared normal there were many which showed degeneration and various stages of cytolysis. There were also found large almost completely acellular areas which presented a mucoid appearance and contained the faint remnants of disintegrating granulocytic cells and occasional reticulum cells. The latter were frequently swollen with vacuolated nuclei and frayed or ill-defined cell margins. These relatively acellular areas showed beginning fibroblastic invasion while in still other regions this replacement had given rise to large fibroblastic and fibrotic patches (Fig. 6). These appearances were interpreted as successive stages of radiation osteitis. Occasionally the hyperplastic myelocytic marrow which represents the early stage of radiation osteitis and the fibroblastic and fibrous marrow, representing later stages, could be seen in a single low-power field. The more advanced changes, however, were more frequently seen near the epiphyseal ends.

*Lymph Nodes.* The changes in the lymph nodes were more or less uniform throughout all the animals except for slight quantitative variations. In general all nodes showed a marked depletion of lymphoid tissue, the background of the depleted areas presenting a pale pink staining fairly homogeneous appearance in which the faint outlines of nuclear membranes were discernible. In contrast to this depletion, in some nodes of all animals but especially in those of the rabbit that lived only 3 months, there were islands of proliferating stem cells, many showing active cell division. In a few nodes of this animal, as in many nodes of the other animals, the foci of proliferating stem cells showed degenerative and necrotic changes so that in some places only the indistinct nuclear and cellular outlines remained. Along with this change was observed a marked increase in lymphoblasts of the large, medium and small varieties which in some instances replaced the mature lymphocytes of the lymph nodes (Fig. 6). Even in markedly depleted nodes some hyperplastic follicles still persisted. The slight damage to the mature lymphocytes and lymphoblasts as compared to the marked damage to the stem cells was a striking feature of the lesion. In Rabbits 2, 3 and 4, a varying number of megakaryocytes, normoblasts and myelocytes were found in the lymph nodes. In some instances the sinuses were crowded with these myeloid cells but occasionally small islands of these cells were found in the lymph cords.

In summary, the lymph node changes consisted essentially of an initial hyperplasia and subsequent degeneration of the stem cells resulting in hypoplasia of lymphoid elements along with myeloid metaplasia.

*Spleen.* In general the spleens showed changes similar to those found in the lymph nodes. There was a marked decrease in mature lymphocytes and of the lymphoid follicles and the normal architecture was replaced by numerous primitive cells undergoing degenerative changes similar to those described in the lymph nodes. As a result of this marked depletion the sinuses were found to be widened and empty and presented the appearance

of a spleen from which the cells had been washed. This was especially noted in Rabbit 4. As in the lymph glands islands of myeloid metaplasia were found in the spleens of Rabbits 2, 3 and 4.

The microscopic changes in the teeth and parenchymatous organs will be presented in a future publication.

**Summary and Discussion.** It has been shown by Seil, Viol and Gordon[6] that 60 to 98% of the radium taken into the human system is eliminated, principally in the feces (90%) and urine (10%). When taken by mouth 65 to 75% is eliminated in the first 4 days and by the 10th day the daily rate of elimination is less than 1%. Thereafter there is a gradual diminution in its removal so that after several years the rate of elimination is down to .002 to .005% per day. In albino rats, Thomas and Bruner,[3] found that 50 to 65% of the radium injected subcutaneously was eliminated within one week of the time of injection. The average retention at the end of 6 to 8 months was 24.6% and 99% of this retained radium was found in the bone ash. We, therefore, feel that it is reasonably safe to assume that in our animals that survived 1 year or longer 10 to 20% of the radium ingested remained in the body tissues and that most of it was fixed in the bone. The animals during life were found to be radio-active by testing with the alpha-ray emanation electroscope.* After death the bones were tested for radio-activity by autophotography[1] that is, by placing the bones on a photographic or Roentgen ray plate for several days. The autophotographs of the radio-active bones of human cases have shown a more or less uniform distribution of radium throughout the skeletal system, although in individual bones the distribution is patchy (Martland[5]). In our Rabbits 2, 3 and 4 a similar patchy distribution in individual bones was noted. The autophotographic areas that showed a decreased radium content were those in which histologic sections revealed the most marked osteoporosis and new bone formation. These observations suggest that the distribution of radium is more uniform throughout all of the bones in the early part of the disease (Fig. 2) while in the later stages as the result of bone absorption and reconstruction the radium content is focally diminished (Fig. 3).

The tissue changes produced in our rabbits by the administration *per os* of radium sulphate may be summarized as follows: gingivitis, alopecia, abrasion of teeth, necrosis of bone, spontaneous fractures, regenerative anemia and hyperplasia and fibrosis of bone marrow. Similar changes and in addition osteogenic sarcoma have been reported in human cases. It is also of interest to note that in our experimental animals as in the human cases the first changes were observed in the jaw and mouth, a condition for which no satisfactory explanation has as yet been advanced. Martland[7] stresses the importance of mesothorium in the production of the extensive

* We are indebted to Dr. Alexander O. Gettler for the electroscopic determinations.

jaw necroses and also the severe anemias in the early acute cases among the radium-dial painters. Our experiments show that changes of a similar nature can be produced by sufficient quantities of radium alone.

Of particular interest are the changes in the blood forming tissues in our experiments since the administration of the radium by mouth was followed by lesions which resemble closely the changes that have been observed in human cases. Our observations would seem to indicate that in the bone marrow radium poisoning produces at first a stimulation of the cells of the erythroblastic series with a preponderance of normoblasts, an effect which is to some extent reflected in the blood picture of this period. Continued action of the radium inhibits maturation of the erythroblasts as evidenced by a slight increase in the number of erythroblasts (Rabbits 3 and 4) despite a decided decrease in the total bone marrow erythrocytic elements. At this stage there is an extensive replacement of erythroid elements by cells of the granulocytic series with the production of the picture of the so-called "replacement anemia."

It is noteworthy that, in the more advanced cases of our series, granulocytic hyperplasia with a preponderance of myelocytes was the outstanding feature of the bone-marrow picture (Table 1), a finding at variance with the observations of Sabin and her collaborators[2] who state that the fact that the bone marrow as a hemopoietic organ is less sensitive than the lymph nodes is shown not only by the lack of change in the granulocytes but also by the slight changes in the red cells.

We were fortunate in being permitted to compare our histologic sections with those of Martland's[7] human series. Aside from the fact that our animals did not develop definite sarcomatous lesions the histologic changes found in the bones and bone marrow of the rabbits showed a striking similarity to those seen in the human cases. This author observed a myeloid hyperplasia which he likens to a "panmyelosis, mimicking multiple myeloma." He found that the majority of the cells of the altered marrow were premature stem cells—"hemocytoblasts, proerythroblasts, and promyelocytes." He saw practically no neutrophilic myelocytes or their mature derivatives, whereas neutrophilic myelocytes constituted the majority of the cells in the hyperplastic marrow of our Rabbits 3 and 4. He found that the only cells of the granulocytic series which approached or proceeded to maturation were the eosinophilic myelocytes which were present in large numbers in the bone marrow but did not appear in the circulating blood. We noted a moderate increase of these cells in the bone marrow especially of Rabbit 4 but also found an increase in eosinophils of the blood.

In contrast to these proliferative lesions in the marrow we also found areas of cellular fibroblastic tissue and acellular fibrous tissue replacing the hyperplastic marrow in Rabbits 2, 3 and 4. These

changes correspond in general to those described by Martland[7] as stages of radiation osteitis, namely, a first or "hyperplastic marrow" stage, a second stage of "cellular replacement fibrosis" and a third or healed stage of "replacement by non-cellular fibroblastic tissue." We did not see any sarcomatous areas arising as he suggested from the cellular fibroblastic tissue, but did observe suspicious areas of hyperplastic fibrous tissue in the periosteal region of the atypical healing calluses. However, because similar areas are frequently found in the vicinity of healing simple fractures and since no metastases could be demonstrated we do not feel justified in designating the condition as osteogenic sarcoma.

The earliest change observed in the lymph nodes was a marked and uniform hyperplasia of the stem cells. Even during this hyperplastic stage degenerative changes were seen in these cells, some showing nuclear damage, while others were found in various stages of cytolysis. In the 3 animals that lived for 12, 13 and 18 months after radium administration, aside from the changes just described there was a decided increase in lymphoblasts in some nodes. The lymphoblasts and mature lymphocytes showed only slight degenerative changes as compared with the marked damage noted in the stem cells. In still other lymph nodes there was found a diffuse depletion of the lymphoblasts and mature lymphocytes and, in some instances, an almost complete atrophy. The earlier lesions in the lymphoid tissue were evidenced by a rise in the number of circulating lymphocytes that began approximately 3 months after cessation of radium administration. This rise was sustained except for slight remissions for approximately 6 months and was followed by a steady fall of lymphocytes with an absolute lymphopenia in the later stages (Graph 1).

The effects of radium on the lymphoid tissue in our experiments may well be divided into the three stages designated by Sabin and her co-workers[2] as "first, a period of stimulation to the stem cells; second, a shift to the immature stage known as the lymphoblast; and third, a depletion of the nodes due to such a damage to the stem cell that the losses in lymphocytes can no longer be made up."

Associated with marked myelocytic hyperplasia of marrow in our more advanced cases should be mentioned the development of myeloid metaplasia in the lymph nodes and spleen, a combination of lesions that perhaps bears a significant relationship to the occurrence of myelogenous leukemia in humans unduly exposed to Roentgen rays or radio-active substances. Rolleston,[8] on the other hand, in his critical review of the literature concerning the harmful effects of irradiation expresses the opinion that the development of leukemia among Roentgen ray and radium workers is probably purely coincidental.

**Conclusions.** 1. The general features of radium poisoning as observed in human cases have been reproduced in rabbits by oral administration of radium sulphate.

2. Jaw necrosis, a characteristic of the early acute cases among radium dial painters, can be produced experimentally by radium alone without mesothorium.

3. In the bone marrow striking changes are produced, consisting of an early hyperplasia of the erythropoietic elements followed by a decreased maturation of the erythroblasts and the replacement of these elements by myelocytes. Finally this hyperplastic marrow is replaced by fibrous tissue.

4. In the lymph nodes there is noted an initial stimulation of the stem cells with subsequent damage to these cells resulting in depletion and atrophy of the lymphoid tissue. In the circulating blood an absolute lymphopenia is found.

5. The development of myeloid tissue in lymph nodes and spleen associated with the extreme myelocytic hyperplasia in the marrow of our animals suggests that the occurrence of leukemia in Roentgen ray and radium workers may not be a pure coincidence.

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## TETRALOGY OF FALLOT (EISEMENGER TYPE) WITH HYPOPLASIA OF THE DEXTROPOSED AORTA

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An exact forecast of the cardiac lesions that may be found in congenital cyanosis was long considered practically impossible, and the idea, that in morbus ceruleus interauricular septal defect must

always be present, died hard. The profession is greatly indebted to Fallot[1] who, in 1888, published a series of articles on the subject In the course of some years he had seen 3 patients come to autopsy, and was struck by the similarity of the lesions. Following this he collected in all 55 cases, in whom 41 (74%) showed that congenital heart disease associated with cyanosis, especially in adults, is the result of a small number of perfectly definite cardiac malformations. This group of pathologic-anatomic aberrations is represented by the following tetralogy: pulmonary stenosis, interventricular septal defect, deviation of the origin of the aorta to the right, hypertrophy of the right ventricle, almost always concentric in type. Patency of the foramen ovale is entirely an accessory defect. He believed that these 4 anomalies arose in consequence of the stenosis of the pulmonary artery. Others now think that the dextroposition of the aorta may be quite as important an element in their origin. This is borne out by the case reported by Baumgartner and Abbott[2] and the one we report. In these cases there was no real pulmonary stenosis but there was dextroposition of the aorta. In only 1 case of Fallot's series was early cyanosis in this tetralogy wanting,[3] and that might be explained by the fact that the obstruction was in the conus rather than in the pulmonary artery, whose opened and unopened valves were intact. Since this obstruction had an opening the size of a little finger, it may have sufficed for the need of the patient.

It is gratifying to have Dr. Paul White[4] include a translation of Fallot's conclusions in his textbook. It is a recognition of Fallot's distinct contribution to the diagnosis of congenital cyanosis, especially those reaching adult life.

In 1897 Eisemenger[5] reported a case which is sometimes referred to as the tetralogy of Eisemenger, which might better be called the tetralogy of Fallot, Eisemenger complex, as suggested by Dr. Maude Abbott. In this patient, a man of 32, with cyanosis since birth, the findings were interventricular septal defect, dextroposition of the aorta, which was placed astride the septa defect so as to receive blood from both ventricles, right ventricular hypertrophy, a moderately widened pulmonary conus arising normally from the right ventricle, and a somewhat dilated pulmonary artery showing some endoarteritic thickening, but whose valves were smooth and competent. He gives no measurements, but since he says the conus is moderately widened and the pulmonary artery is somewhat dilated, it is inferred that the dimensions were not striking. The aorta was of its usual dimensions, thin walled and smooth. There was no pulmonary stenosis in this case.

Baumgartner and Abbott[2] reported a case of the Eisemenger type in a man of 20 who was found to have an interventricular septal defect, dextroposition of the aorta, with a pulmonary conus, orifice and artery normally developed, but having undergone "dilatation

as a result of influx of blood from the left ventricle through the defect into the pulmonary circulation." They stress the fact that there was no pulmonary obstruction in this case.

The case we present was that of a woman, aged 31, with cyanosis since birth whose heart showed interventricular septal defect, a slightly widened conus arteriosus and a fusiform dilatation of the pulmonary artery; a hypoplasia of the dextroposed aorta, which was so placed as to receive blood from both ventricles; great hypertrophy and dilatation of the right ventricle. The hypoplasia involved both the thoracic and abdominal aorta. The foramen ovale was intact in this case, as it was in Eisemenger's. Here again is a case of tetralogy of Fallot, Eisemenger type, in which there was marked pulmonary dilatation and insufficiency and little, if any, obstruction.

**Case Report.** The patient, aged 31, of German-American parentage, was 61 inches tall and her weight over a 9-year period ran from 96 to 108 pounds. She was well developed both physically and mentally. Her mother stated that she was born at 8 months and was a blue baby. Her mother never had any rheumatic fever or any other infection, at least during the pregnancy. There is 1 brother who is 37 and in good health.

Her early infections were measles and chickenpox. She had double mumps in 1926 and pertussis the same year. Her tonsils from 1929 on were evidently somewhat infected. Her thyroid was palpable but had no influence on the condition. Her teeth were always good. She had bronchopneumonia twice, and was given to attacks of bronchitis. Always throughout life she suffered from dyspnea on exertion. Up until 9 years she was considered a delicate child, after that she was active, taking part in sports and dancing until she was 15. Her periods began at 12; they were usually profuse, sometimes irregular, and at 15 she had a marked menorrhagia and was admitted to a hospital with the diagnosis of mitral stenosis and a blood count of hemoglobin, 50%; red blood cells, 3,420,000; white blood cells, 6000. After curettement she recovered and was not troubled overmuch by her heart condition until after the birth of her first child in 1924. This child is a perfect specimen of boyhood. After his birth she noticed she had less cardiac reserve, which was still further lowered in September, 1926, when she gave birth to twins at 7 months, who survived but 6 hours. Although she had always shown cyanosis from birth it was worse after these pregnancies. It involved her visible mucous membrane, lips, cheeks, ear tips, fingers and toes and the latter both showed clubbing. Epistaxis was a frequent occurrence and sometimes it was severe as in 1927 and 1930. She was blind for 2 hours after labor in 1926. She had much vertigo and many fainting fits and was once carried unconscious into a hospital from the street. She was always more or less hoarse and it was especially marked after 1926. The postmortem findings confirmed Fetterolf and Norris,[6] who maintained that the recurrent laryngeal paralysis was due to pressure of the enlarged pulmonary artery rather than the enlarged left auricle. The highest early blood count was in 1926 when the hemoglobin was 120%; red blood cells, 5,750,000; white blood cells, 7500. Three counts made in 1928–1929 all showed hemoglobin of from 105 to 110% and red cells over 5,000,000. From that time on until her last illness the counts were nearer normal. The average of many counts was hemoglobin, 88%; red blood cells, 4,350,000; white blood cells, 7830. November, 1934, she developed an acute respiratory infection with a severe cough. This led to marked

failure by congestion and with the consequent passive engorgement the counts rose again. Because of the severity of her condition, through the courtesy of Dr. E. W. Pflueger, who was attending her, she was admitted to the Presbyterian Hospital 18 days before her death. On admission the count was hemoglobin, 140%; red blood cells, 6,250,000; white blood cells, 7800. The average of 4 counts after that was hemoglobin, 120%; red blood cells, 5,620,000, although 200 to 300 cc. of blood were withdrawn before each intravenous injection of an equal amount of glucose solution.

*Physical Examination.* This is largely a composite picture of the important and more or less constant findings over a 9-year period.

There was usually an epigastric impulse and an exaggerated movement to the left of the sternum about the 3d and 4th ribs. The midsternal thrill was systolic and sometimes diastolic. At the 3d left intercostal space there was sometimes a diastolic thrill. Percussion showed a wide lateral diameter of the heart and increased dullness in the region of the left auricle and pulmonary artery. The first sound at the apex was always short, sharp, exaggerated and snapping; occasionally it was doubled. The second pulmonary sound was usually recorded plus, the aortic second sound was often marked plus and sometimes simply present. The second sound at the apex was usually present. A low pitched diastolic murmur was constantly heard at the pulmonary cartilage and at the apex. This diastolic murmur could be traced from the pulmonary cartilage along the left edge of the sternum to the apex. Sometimes there appeared to be a gap in tracing this murmur, so that it suggested that there possibly was a second diastolic murmur at the apex. Sometimes we thought there was a presystolic exaggeration. There was a systolic murmur at the apex higher pitched, heard also over the midsternum but not transmitted, at least regularly, to the base of the heart. Occasionally a slight transmission to the axilla and the left back is recorded. Only once was there a systolic murmur at the pulmonary area found. It is interesting that the abnormal valves found at postmortem should not have produced a more constant systolic element; the diastolic murmur was never lacking.

The fluoroscopic examination, in 1929, showed an enlarged shadow lying in the region of the great vessels beginning at the level of the 2d rib and extending downward to the 4th rib anteriorly where it joined with the left ventricular shadow. This mass pulsated and the aorta appeared to be posterior to it. The right side of the heart was greatly enlarged. The great vessels measured 9 cm., the heart's transverse diameter was 14.5 cm. and the chest 27 cm.

Again in 1931 the pulmonary artery and right ventricular conus were unusually prominent and pulsated freely.

The films showed as early as 1927 a marked bulging in the upper left segment of the heart silhouette, a rounded enlargement of the right ventricular border and a markedly increased transverse diameter of the heart giving the ventricles a globular shape. This hypertrophied right ventricle pushed the conus pulmonalis upward and this with a widened pulmonary artery gave the prominent pulmonary arc in the curves.

The silhouette (Fig. 1) is much like that of Vaquez and Bordet[7] of their young woman of 25 who had pulmonary stenosis and interventricular septal defect but no cyanosis.

The silhouette of Baumgartner and Abbot's case also shows an exaggerated pulmonary segment in the film, and a globular shadow of the ventricles with increased transverse diameter.

There were many electrocardiograms, they were all essentially like the cuts (Fig. 2). The deflections were rather large, there was never the picture of preponderance that one would have expected, there were some premature beats and for a short time once there was auricular fibrillation. The *Q–R–S* deflections were usually larger than normal, suggesting congenital heart disease. *P*2 and *P*3 often suggested auricular hypertrophy. Figure 3 shows ventricular asynchronism. As Petit[8] puts it, the two ventricles do not contract simultaneously. The *Q–R–S* presents successively the characteristic predominance of one or the other ventricle and takes on a diphasic aspect. In the *Q–R–S* of Figure 3, in the first phase there is a deep *Q*1 and a tall *R*3 as in predominance of the right ventricle. In the second phase there is a tall *R*1 and a deep *S*3, the sign of a left ventricular preponderance. He thinks that the succession of the two predominances can only be explained by ventricular asynchronism, in this case the right predominance preceding. The exaggerated hypertrophy of the right ventricle makes this easy to understand. The electrocardiogram confirms the clinical findings of a doubled first sound at the apex at times.

**Discussion.** The first impression of everyone on examining the patient was that mitral stenosis was a part of the picture. The short, sharp, exaggerated first sound, the diastolic murmur at the apex, the exaggerated pulmonary second with the very marked diastolic murmur at the pulmonary cartilage suggested a mitral stenosis with a Graham-Steell murmur of pulmonary insufficiency. Real congenital mitral stenosis is rare,[9] and in a cyanotic subject is apt to be associated with patent ductus arteriosus which we felt sure we did not have in this case.

The cases of mitral stenosis with interauricular defect of Lutembacher[10] did not help because in this condition cyanosis is usually late.

The early and high degree of cyanosis and the comparative frequency of tetralogy of Fallot as the underlying cause made a better prospect. The prominence of the right ventricle and of the pulmonary segment, especially in the Roentgen ray picture, suggesting interventricular defect and pulmonary stenosis were helpful. The lack of a constant systolic murmur at the pulmonary cartilage and the constant presence of a diastolic murmur there, made us feel that pulmonary insufficiency was sure and that pulmonary stenosis was absent or of a very mild degree.

Any broadening of the aortic shadow to the right of the median line was not found, though of course we did not suspect hypoplasia of the aorta. Dr. Fowler's report of the postmortem shows that the diagnosis of tetralogy of Fallot was confirmed, but in addition there was the unexpected hypoplasia of the aorta.

*Postmortem Examination.* The postmortem examination presented a well developed and well nourished white female of 31. The skin showed

FIG. 1.—Silhouette (6 feet) of heart and great vessels, showing great prominence of pulmonary arc (*P*), a wide transverse diameter, an enlarged right ventricle, and globular shape of ventricles.

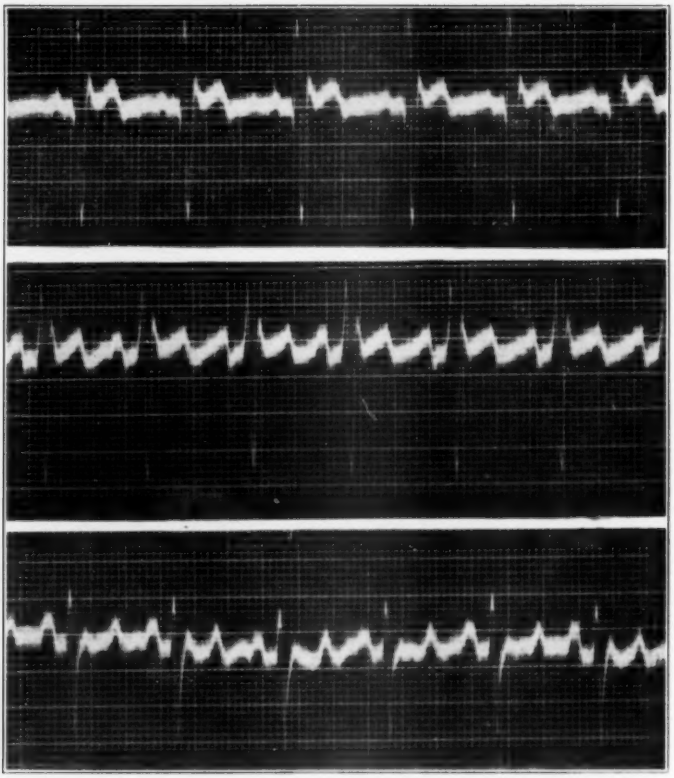

FIG. 2.—Taken December 6, 1928. This is a fair sample of the average curve. The amplitude of *Q–R–S* in Leads I and II suggests congenital heart disease. *P2* and *P3* are quite prominent.

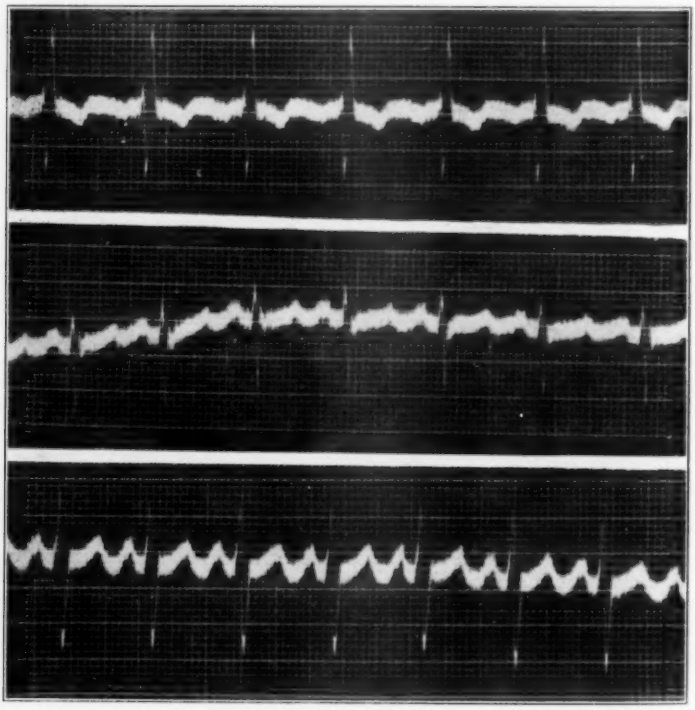

FIG. 3.—Taken February 7, 1929. Shows ventricular asynchronism.

a dusky cyanosis. The fingers were markedly clubbed. Half a liter of clear fluid was found in the left pleural cavity. The lungs were wet and congested.

The pericardial cavity contained 350 cc. of bloody fluid. The transverse diameter of the heart was 15 cm. The heart was globular in shape, the apex being formed by the right ventricle (Fig. 4). The weight was 500 gm.

There was dilatation and hypertrophy of the right ventricle. The wall of the right ventricle was 1.5 cm. thick. The conus arteriosus was slightly widened and markedly thickened. The pulmonary orifice measured 10 cm. in circumference (Fig. 5). The pulmonary cusps were thickened, of unequal length, and the margins were rounded. The left anterior one was fused with the posterior one. The right anterior cusp was voluminous. There

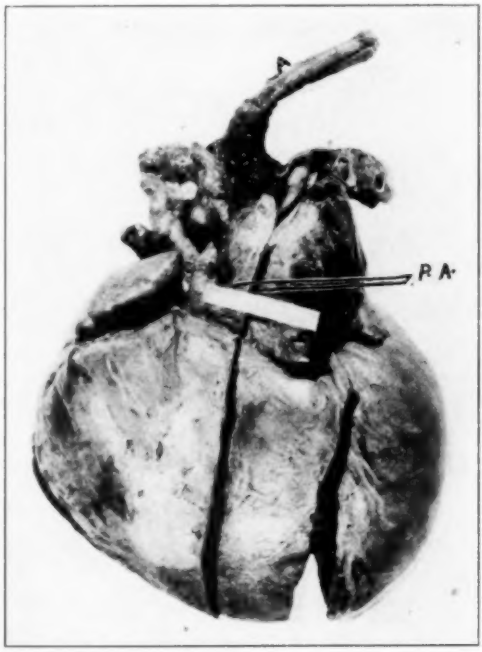


FIG. 4.—Heart showing globular shape, transposition and hypoplasia of aorta (*A*), and dilated pulmonary artery (*PA*).

was a fusiform dilatation of the pulmonary artery, the greatest circumference of which was 10.5 cm., and there was a moderate atherosclerosis. There was a ragged tear 3 cm. in length in the intima of the pulmonary artery just above the orifice. Blood had extravasated into the media and adventitia.

The left ventricle was dilated, but not to the extent seen in the right ventricle. The wall was hypertrophied, measuring 3 cm. in thickness. The aorta appeared displaced to the right and somewhat rotated on its axis so that it overrode an interventricular defect 2.5 by 2 cm. in the anterior portion of the pars membranacea septi (Figs. 5 and 6). The interventricular septum measured 2 cm. at its thickest part.

There was marked hypoplasia of the aorta. The circumference of the aortic ring was 5.5 cm. The greatest circumference of the arch was 4.5 cm.

and of the thoracic aorta 3 cm. The aortic cusps appeared normal, the lining smooth.

The leaflets of the mitral and tricuspid valves were normal except for a slight thickening. The rings of these valves were 12 and 13 cm. in circumference respectively. The atria showed no remarkable features.

The *liver* was enlarged and weighed 2100 gm. On section the parenchyma was wet and a dark red color. There was marked dilatation of the veins and arteries throughout the parenchyma of the liver.

The *gall bladder* appeared normal.

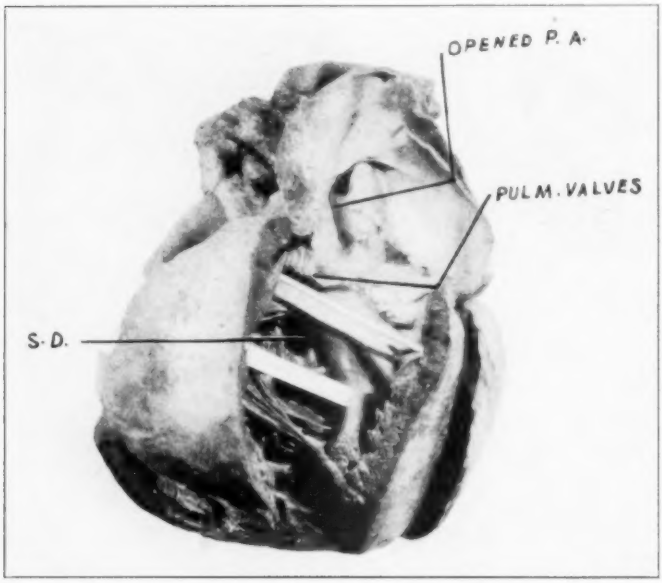


FIG. 5.—Opened right ventricle, showing hypertrophy of wall, scarring of pulmonary leaflets, marked widening of opened pulmonary artery (*Opened P.A.*) and septal defect (*S.D.*).

The *spleen* was enlarged and weighed 250 gm. The capsule was tense and stretched. On section there was seen an infarct on the diaphragmatic surface of the spleen. Parenchyma was firm and a dark red color.

The *pancreas* grossly appeared normal.

The *kidneys* weighed 350 gm. together. Their capsules stripped off with ease. On section the cortex was of normal thickness and a pale red color. The calyces and pelves were normal.

The *uterus* and *adnexa* showed no unusual features.

The *urinary bladder* was empty.

Examination of the *gastro-intestinal tract* showed no pathologic condition.

*Microscopic Examination. Lungs.* Sections show many of the alveoli filled with blood, heart failure cells and fluid. Some sections show a considerable increase in the interstitial connective tissue. The bloodvessels throughout the parenchyma are dilated.

*Heart.* Sections through the right and left ventricles show the nuclei of the muscle fibers to be larger than normal. There is some increase in

connective tissue throughout the myocardium. There are a few focal areas of lymphocytic cell infiltration scattered throughout the myocardium.

*Pulmonary Artery.* The media is composed of a rather hyalinized connective tissue. The adventitia is infiltrated with extravasated blood.

*Aorta.* Gross sections show no unusual features except the aorta is considerably less than normal thickness.

*Liver.* There is a marked dilatation of the central veins and arteries. The hepatic sinuses surrounding the central veins are dilated. The hepatic cells appear atrophic in character.

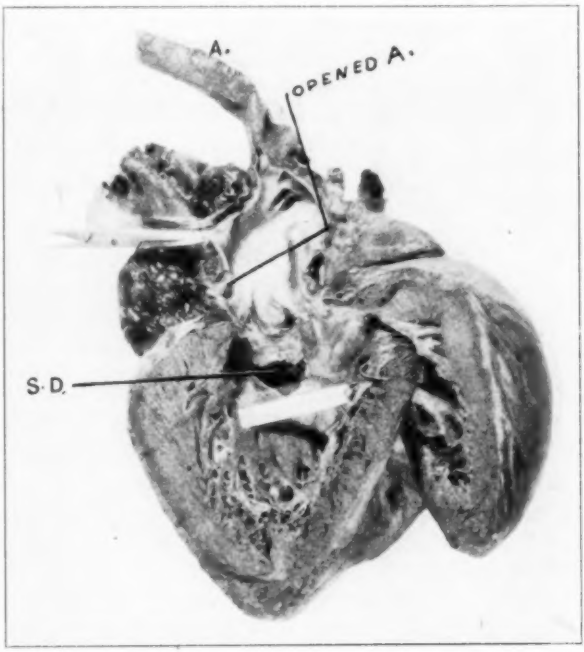


FIG. 6.—Opened left ventricle showing hypertrophy of wall, septal defect (*S.D.*) and opened hypoplastic aorta (*Opened A.*).

*Spleen.* Sections through the infarct show degeneration and necrosis of the splenic pulp. The adjacent parenchyma shows marked congestion of the pulp.

*Kidney.* The glomeruli diffusely throughout the sections appear large, cellular and congested. The bloodvessels throughout the cortex and medulla are dilated. There is slight tubular degeneration.

*Pancreas.* Sections show no marked changes from normal.

*Adrenal.* There is slight hydropic degeneration of the cortex.

**Summary.** The patient, a woman a little over 31 when she died, was born at 8 months and was a "blue baby." She had a normal physical and mental development, passed through two pregnancies and was able to take care of her house until within a month of her

death. The diagnosis of tetralogy of Fallot, with the incompetency of the pulmonary valves was confirmed at postmortem. In addition there was a hypoplasia of both the thoracic and abdominal aorta, which was not suspected.

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## COARCTATION OF THE AORTA WITH INTERMITTENT LEAKAGE OF A CONGENITAL CEREBRAL ANEURYSM.

### Report of a Case.

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Coarctation of the aorta implies a partial or complete occlusion of the lumen of the aorta and when it affects an adult, it occurs at or near the insertion of the ductus arteriosus, which is usually just distal to the origin of the left subclavian artery. Blackford found that, in a series of 68,300 consecutive necropsies reported by 6 authors, coarctation of the adult type occurred 43 times or an incidence of 1 in 1588 necropsies. Less than 350 reports of this anomaly are to be found in the literature, and the condition was diagnosed clinically in less than a fourth of these cases. These statistics clearly indicate that coarctation of the aorta exists far more frequently

than is clinically appreciated. However, there has been a very noticeable increase in the number of cases reported within the past 5 years.

The etiology and pathogenesis of this condition have been adequately reviewed by Abbott and by Blackford, and need not be considered here. Congdon has added much to the understanding of the pathogenesis of cardiovascular anomalies by his contribution on the embryologic development of the aortic-arch system.

Bonnet has divided coarctation of the aorta into the infantile and adult types. The infantile type is merely a narrowing of the isthmus of the aorta and may be considered as a persistence of the anatomic relations that existed under the conditions of fetal circulation. This type has little clinical significance as the victims are all doomed to an early death.

In the adult type, a pathologic condition is found which has no counterpart in intrauterine existence. The findings which are usually quite typical are well illustrated in Fig. 1. This specimen was obtained at necropsy of a case observed by one of us (Shelden). This case previously was included in the series collected by Blackford. The aorta appears as though it had been ligated at the point of constriction. An hour-glass bulge is usually present above and below the constriction, and the ascending portion may be the seat of an aneurysmal sac. Occasionally, the aorta may be hypoplastic throughout. Cardiac hypertrophy occurs in 75% of the cases (Blackford), and bicuspid aortic valve is present in 25% of cases (Abbott). Other anomalies of the great vessels of the aorta and of the cerebral vessels are frequently encountered. The innominate and subclavian arteries and their branches, together with the arteries which are usually responsible for collateral circulation, namely the first three intercostal, the dorsalis scapular, the internal mammary, and the deep epigastric arteries, are markedly dilated in most cases. Other arteries may assist in collateral circulation.

**Diagnosis.** The diagnosis is not a difficult one, and is not dependent on laboratory or roentgenographic confirmation, although the latter is frequently helpful. In the great majority of cases the patients are robust young adults who have led an active life and frequently have participated in athletics. The latter observation has been attributed by some writers to the increased cerebral circulation. Because of the paucity of symptoms, the physician is frequently not consulted until the signs of cardiac insufficiency or an unexplained cerebral hemorrhage has occurred. The seriousness of the complication may make a thorough examination impractical so that coarctation of the aorta may not be recognized as the contributing factor. Intermittent claudication or "poor circulation" is occasionally the presenting complaint.

The signs of coarctation of the aorta are quite definite and once the diagnostic features are discovered, the clinical diagnosis is

almost always substantiated by necropsy. The cardial signs may be summarized as follows:

1. A forceful, bounding pulse is noted in the vessels of the neck and upper extremities, and an absence or marked diminution of pulsation, in the vessels of the lower extremities. If a feeble pulse is detected over the femoral arteries, it is asynchronous with the radial pulse.

2. A palpable aortic pulsation is absent in the abdomen whereas a forceful systolic thrust is present in the suprasternal notch.

3. There is hypertension in the brachial arteries, usually with a definite pulse pressure and a much lower blood pressure in both popliteal arteries. This is a reversal of the normal state.

4. Evidence of a well-developed collateral circulation is found. Large, tortuous, anastomosing arteries may be seen and palpated in the interscapular, suprascapular, and axillary regions, and less often are conspicuous over the anterior aspect of the thorax. The internal mammary and deep epigastric arteries are occasionally visible and palpable. These collateral vessels transmit a systolic or presystolic murmur and frequently a fine accompanying thrill.

5. A murmur, which is usually heard over the aortic area, has its maximum intensity along the left border of the sternum. This murmur is frequently altered by the congenital or acquired valvular lesions which may be present. Cardiac hypertrophy is present in three-fourths of the cases.

While the diagnosis is essentially a clinical one, certain accessory roentgenologic signs are of value when present. They are as follows: (1) a bilateral erosion of the inferior borders of the ribs; (2) an absence of the prominent aortic knob, usually associated with hypertension; and (3) a dimpling of the descending aorta, which is best seen in the left oblique position.

**Association of Cerebral Aneurysms With Coarctation.** The frequency with which cardiovascular anomalies, such as a bicuspid aortic valve, defects of the aortic septum, subaortic stenosis, persistent left superior vena cava, anomalous origin of the arteries from the aortic arch, and congenital cerebral aneurysms, are associated with coarctation would almost appear to be a significant part of the picture. Of these associated anomalies, only the cerebral aneurysm presents a grave source of potential danger.

Eppinger, in 1887, first suggested rupture of a congenital aneurysm of the cerebral arteries as an explanation of cerebral hemorrhage of unknown etiology, particularly in young adults. He says that "in the small and smallest arteries, like those forming the circle of Willis and its branches, many aneurysms have a congenital origin and are due to an inborn defect of the arterial wall." Many observers have since reached the same conclusion, and it is generally agreed that rupture of a congenital cerebral aneurysm must be considered as an explanation in any "spontaneous" cerebral or meningeal

hemorrhage which affects a non-hypertensive individual, particularly a young person. Except in rare instances, these small aneurysms are not dependent on infection. Fearnsides reported that only 6% of the aneurysms of the small cerebral arteries can be proved to have a possible syphilitic basis, and these largely occur in the basilar and vertebral arteries. Aneurysms of the cerebral vessels, which are of syphilitic origin, usually attain sufficient size to produce symptoms that simulate tumor of the brain, while the aneurysms of congenital origin are often very small and usually do not give rise to symptoms until intermittent leakage or rupture occurs. Forbus and others in studying these congenital cerebral aneurysms found an absence of the media of the arterial wall at the bifurcation of the cerebral vessels from the circle of Willis, where the great majority of these aneurysms are found. Forbus also demonstrated that a greater pressure is exerted on the arterial wall at the angle of bifurcation than elsewhere. It is, therefore, not surprising that, in cases of coarctation of the aorta in which there has been a sustained hypertension in the cerebral vessels since early life, we should frequently find these congenital aneurysms, and that "spontaneous" cerebral or meningeal hemorrhage is the cause of death in a relatively high percentage of these cases.

Woltman and Shelden found that in 32 cases of coarctation of the aorta with neurologic complaints, in which necropsy was performed, cerebral hemorrhage was responsible for death in 37.5%. This complication was also found to be the cause of death in 17% of the cases in the series collected by Blackford. Abbott, in 1928, collected the reports of 20 cases of coarctation of the aorta, in which cerebral hemorrhage was the cause of death. In 7 of these cases, a ruptured congenital aneurysm was definitely demonstrated to be the source of hemorrhage. She said: "In view of the extreme difficulty and sometimes the impossibility of locating these very small, almost miliary aneurysms, on the cerebral vessels in the midst of a large hemorrhage at the base, and the extreme youth of most of the patients so dying in this series, it seems safe to conclude the presence of a ruptured cerebral aneurysm in practically all such cases of so-called spontaneous cerebral hemorrhage occurring in coarctation before the end of the second decade without a history of infection or other apparent cause."

Eppinger (1887), Kolisko (1913), Strassmann (1922), Woltman and Shelden (1927), Parkes Weber (1927), and Green (1928) have reported cases of coarctation of the aorta in which necropsy revealed that the spontaneous cerebral hemorrhage was clearly the result of a ruptured aneurysm of the cerebral vessels.

Parker, in 1926, emphasized the phenomenon of "intermittent leakage" as a diagnostic sign of a small rupture in the aneurysmal sac, in which the small, slitlike aperture closes following a certain amount of bleeding. He said: "Much more interesting clinically

are the cases of intermittent leakage of blood from the aneurysmal sac with alternating episodes of disturbed function and periods of relatively good health. . . . In these cases, there was a history of two, three, or more apoplectiform seizures separated by varying intervals. At necropsy the pathologic counterpart of these episodes was found in different layers of old and recent hemorrhage from a ruptured aneurysm at the base of the brain. This general behavior is characteristic and diagnostic in a large percentage of cases of intracranial aneurysms and makes it possible to recognize the disease during life. The onset of these attacks is usually sudden and associated with sudden severe headache or sensation of something giving away in the head."

Lichtenberg and Gallagher have reported the only case of coarctation of the aorta associated with intermittent leakage of a cerebral aneurysm diagnosed during life. Their patient, who was a girl, aged 12, was still living 18 months after the cerebral accident. It is our purpose to record a similar case in which the association of these two anomalies has been diagnosed during life.

**Case Report.** *History.* A married woman, aged 25, came to the clinic on April 17, 1935, complaining of a recent diplopia and hypertension. Prior to July, 1934, she had always enjoyed exceedingly good health and had indulged strenuously in tennis, hockey, basketball, and swimming. Pertussis was the only illness which the patient recalled with the exception of a traumatic injury to the back, which had occurred in 1933. There was no history of rheumatic fever or syphilis and she knew of no other cases of hypertension in the family.

In July, 1934, after swimming for almost 2 hours, she had experienced a "sudden, bursting sensation in the head," which had been followed immediately by a violent headache over the right temporal region, blurred vision, vertigo, and generalized weakness. She had not lost consciousness. She said that she would have drowned if the occupants of the accompanying boat had not seen her plight and pulled her from the water. The headache and vertigo had persisted for 2 hours. She had consulted her physician a few days later, at which time the value for her systolic blood pressure had been found to be 185 mm. of mercury. This had been the first knowledge of her hypertension.

She had then felt perfectly well until March 15, 1935, when a severe, throbbing, pulsating headache had developed. This had been localized over the right temporofrontal area. The headache had been present almost constantly for 2 weeks; it usually had been accompanied by dizziness, nausea, and occasionally by blurred vision. The value for the blood pressure was found to range as high as 220 mm. of mercury at this time.

On April 8, 1935, she had experienced a syncopal attack, which had been preceded by a sudden loud noise in the head and a severe pulsating headache. The syncope had lasted less than 5 minutes and so far as the patient was aware, it had been unaccompanied by any significant features.

On April 13, 1935, while purchasing a few articles at a drug store she suddenly had lost all vision in the right eye. This attack also had been followed by severe headache and dizziness but there had not been any hemiplegia, loss of consciousness, disturbances of speech, paresthesia, and so forth. She had noticed some return of vision after 3 hours, and 4 days later the vision had been found to be normal. Diplopia, dilatation

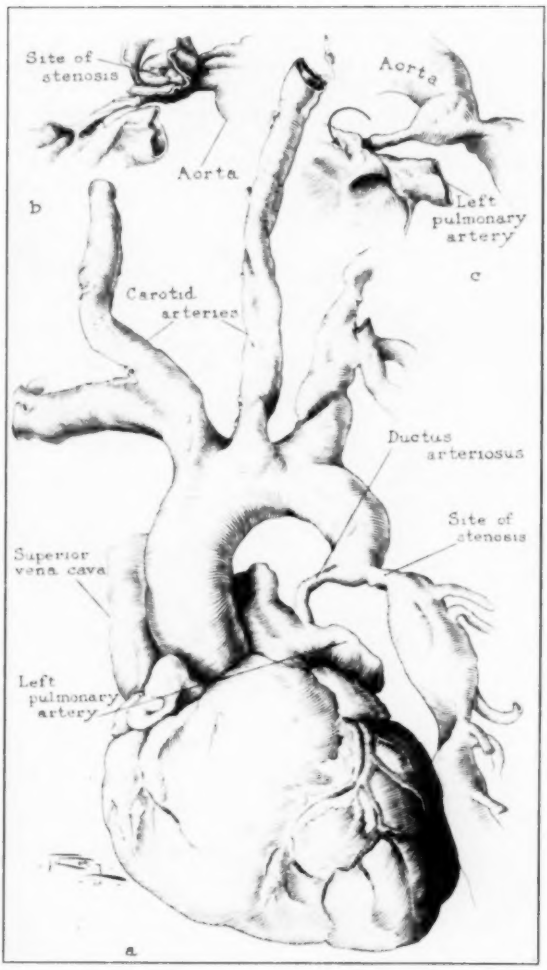


FIG. 1.—Gross pathologic changes in coarctation of the aorta (case observed by Shelden).

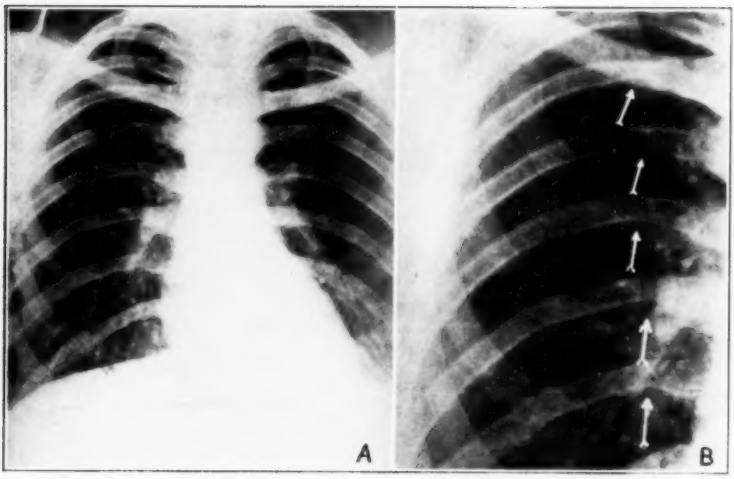


FIG. 2.—*A*, Bilateral erosion of the ribs posteriorly, absence of the shadow of the aortic knob and normal cardiac shadow in the case reported; *B*, arrows indicate areas of erosion of ribs produced by dilated intercostal arteries.

of the right pupil, and slight ptosis of the right lid had been noticed with the return of vision. She came to the clinic 4 days after this episode.

*Physical examination* revealed a young woman, who was well developed and of an athletic build and who weighed 136 pounds (61.7 kg.). The lungs, abdomen, and pelvis were essentially normal. The tonsils were large and cryptic but not obviously diseased. The thyroid gland was moderately full. The pulse and temperature were normal.

The heart was apparently not enlarged, but auscultation revealed a well-defined double murmur over the aortic valve, with its maximal intensity transmitted along the left border of the sternum. The radial pulse in each arm was forceful, sudden, relapsing, and of the Corrigan type. The value for the systolic blood pressure in the right arm was 182 mm. of mercury and that for the diastolic was 82 mm. of mercury, revealing the high pulse pressure of aortic insufficiency. A slight capillary pulse in the nail beds was present. In attempting to elicit the Duroziez "pistol-shot" sound over the femoral arteries, the clue to the correct diagnosis was found. There were no pulsations over either femoral artery. This was substantiated by totally absent pulsations of the posterior tibial, dorsalis pedis, and popliteal arteries in both legs, but because of an apparently adequate collateral circulation, there was no pallor of the lower extremities with elevation, or rubor with dependency. There was likewise no palpable pulsation of the abdominal aorta although the vertebral column could be palpated with ease. The pulse in the carotid, brachial, ulnar, and radial arteries was full and bounding.

The blood pressure was taken in the recumbent position and the values in millimeters of mercury were as follows: for the right brachial artery: systolic 182, diastolic 82; for the left brachial artery: systolic 176, diastolic 74; for the right popliteal artery: systolic 118, diastolic ?; for the left popliteal artery: systolic 128, diastolic ?. The sounds were heard with difficulty over the popliteal vessels and the oscillations of the manometer were barely perceptible.

No visible pulsating vessels over the thorax were observed. There were, however, several palpable vessels in the interscapular regions of both sides and the murmur could be heard over all of the upper intercostal arteries and over the dorsalis scapular arteries in the axillary and posterior aspects of the thorax.

*Neurologic Examination.* On the right side there was a ptosis of the upper lid, a paralysis of the internal rectus muscle, a loss of convergence, and a dilatation of the pupil, indicating a partial paralysis of the oculomotor nerve on the right side.* Reflexes were bilaterally exaggerated but equal. No pathologic reflexes were present. Vision was normal in both eyes and the visual fields were roughly normal. The ocular fundi showed only a slight hypertensive diminution in the caliber of the arteries.

*Laboratory Data.* The Kline and Kahn reactions of the blood were negative. The hemoglobin, blood count, amount of urea in the blood, and the urine were all normal. A blood culture did not show any growth on blood and brain agar within 48 hours.

*Roentgenographic Examination.* A roentgenogram of the thorax revealed a bilateral erosion of the inferior surfaces of the 4th, 5th, 6th, 7th, and 8th ribs posteriorly; the erosion was more pronounced on the right side than it was on the left. The aortic knob was not visualized and there was no cardiac hypertrophy (Figs. 2A and B). A roentgenogram of the head did not reveal any abnormality. Unfortunately, a left oblique roentgenogram of the thorax was not made as it was necessary for the patient to return home before this could be done. An examination of the cerebrospinal fluid was omitted for the same reason.

* Correspondence has revealed that the diplopia persisted for a period of 2 months.

**Comment.** Although frequently overlooked, as the incidence in a large number of necropsies indicates, coarctation of the aorta produces outspoken clinical signs and the diagnosis is not difficult. It requires only a routine palpation of the aorta and the peripheral vessels, a few readings of the blood pressure, and a threshold of suspicion which includes this interesting anomaly as a possibility in any unexplained cardiovascular disease or accident which affects a young adult. In any case in which a patient who is less than 40 years presents signs of cardiac insufficiency without a rheumatic or syphilitic basis, coarctation should be considered. Routine palpation of the peripheral vessels and readings of the blood pressure in the popliteal arteries occasionally will reveal coarctation of the aorta which has masqueraded previously under the diagnosis of essential hypertension. The possibility of coarctation should be borne in mind when the patient complains of intermittent claudication, although the great majority of these patients will have thromboangiitis obliterans or arteriosclerosis obliterans.

Once the diagnosis of coarctation of the aorta is established, any cerebrovascular accident should suggest the possibility of an intermittent leakage or rupture of a congenital cerebral aneurysm, most frequently situated in the circle of Willis, as the association of these two anomalies is not infrequently observed. In the case here presented, it was the neurologic lesion which first called attention to the aortic anomaly. We feel that this patient had suffered two and possibly three episodes of intermittent leakage of a cerebral aneurysm without an actual rupture in the strict sense of the word. She returned home with the advice to discontinue athletics and to avoid strenuous physical activities in the hope of preventing a vascular catastrophe.

Abbott has shown that in 77% of these cases death was the result of coarctation or one of its complications. These complications include rupture of the heart or of the ascending portion of the aorta (20%), cardiac insufficiency (30%), cerebral hemorrhage (12%) mycotic endarteritis and rupture of mycotic aneurysms just below the coarctation (7%), and cardiac asystole without apparent cause (8%). The average span of life is approximately 35 years. By recognizing this anomaly early, much can be done to avert disaster by curtailing physical activities and prohibiting athletics in which, strangely enough, most of these patients strenuously indulge.

**Summary.** A series of an unusually large number of consecutive necropsies indicates that coarctation of the aorta occurs far more frequently than is clinically appreciated. The pathology and diagnosis of this anomaly is discussed and attention is called to the ease with which this diagnosis may be confirmed or denied. The association of congenital cerebral aneurysm with coarctation is emphasized. A case in which coarctation with possible intermittent leakage of a congenital cerebral aneurysm affected a young woman still living is reported.

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## PRIMARY PULMONARY ARTERIOSCLEROSIS WITH POLYCYTHEMIA: ASSOCIATED WITH THE CHRONIC INGESTION OF ABNORMALLY LARGE QUANTITIES OF SODIUM CHLORID (HALOPHAGIA).

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A growing interest in the subject of pulmonary arteriosclerosis has centered in the observation that the phenomenon is apparently the usual, if not the invariable, result of a prolonged elevation of

pressure in the pulmonary circulation. With few exceptions this hypertension has been due to extravascular obstruction to the pulmonary circulation producing what we may call the "syndrome of obstruction" in the lesser circulation—dyspnea, cyanosis, polycythemia and right ventricular hypertrophy. The majority of cases presenting this syndrome reveal an antecedent and probably related cardiac, bronchial or pulmonary abnormality, but there are instances in which such a causative factor is not demonstrable.

The case herewith presented is one which shows extensive sclerosis of the smaller pulmonary arteries. The symptoms of lesser circulatory obstruction were prominent during life. The rôle played by an abnormal appetite for and lifelong ingestion of excessively large quantities of sodium chlorid is questionable. Following a brief discussion of the pathologic changes involved, the clinical features of our case will be considered from two standpoints: first, those which are chiefly of interest in relation to diagnosis, and second, those which are of interest in relation to etiology.

**Case History.** A young woman, aged 20, was first seen in December, 1932, complaining of marked shortness of breath, "pounding of the heart" upon the slightest exertion and an almost constant craving for salt—all present since early childhood; and of more recent origin, vaginal bleeding and inability to sleep.

The patient's parents state that when she was 3 weeks old a definite blueness of the lips was observed but that no other abnormality in the child was noted until she became large enough to climb into a chair and reach objects on a table or sideboard. It was then that an abnormal hunger for salt became manifest and the knowledge of certain punishment would not deter her from appropriating the contents of a salt tumbler. When about 4 years old it was noted that shortness of breath and exhaustion were beginning to prevent the patient from indulging in activities usual to children of that age.

During childhood the patient had pneumonia 6 times, the first attack occurring at 2 years. The susceptibility to frequent respiratory infections was not relieved by tonsillectomy at 12. She never suffered from a chronic cough nor was there ever any suggestion of asthma. When she was 15 she was placed in a girl's school where a positive blood Wassermann was reported to have been found. She was given 3 doses each of mercury and arsenic, then taken home and placed under the care of a dermatologist who could not, however, verify the diagnosis of syphilis. No more treatment was given and blood Wassermann tests continued to be consistently negative at yearly intervals.

In October, 1931, the patient came to the Rocky Mountain region and was married. She had spent her life near sea level and on coming to the higher altitude she noted a marked aggravation of the respiratory distress. In May, 1932, she induced the miscarriage of a 3½ months' fetus following which uterine bleeding persisted until a curettement was done early in December, 1932, by Dr. C. A. Dorsey, who subsequently referred her to one of us (W. D.) for study.

When she was first seen, a short walk was sufficient to induce extreme fatigue with marked dyspnea. For more than a year sleeping had been difficult because of inability to breathe freely on lying down. She stated that she was eating as much as from 2 to 3 pounds of salt a week and that she always carried rock salt with her to consume between meals.

*Physical Examination and Laboratory Findings.* The patient was a well developed, young adult female, with moderate cyanosis of the skin of the face and extremities. There was no clubbing of the fingers or toes. Microscopic examination revealed the skin capillaries at the nail root to be elongated, tortuous and dilated throughout the arterial limb. The eye grounds were a deeper red color than normal with marked dilatation and tortuosity of the retinal veins. The nasal and pharyngeal mucous membranes were markedly cyanotic. The tonsils were absent. The breasts were large and pendulous, extending below the umbilicus. The thorax was of normal configuration. Examination of the lungs revealed no abnormalities to percussion or auscultation. No thrills could be palpated over the precordial area. Percussion of the heart borders revealed moderate enlargement to the right in the fifth interspace and marked enlargement to the left at the base. The heart sounds were labored and a marked reduplication and accentuation of the pulmonic second sound was found. No murmurs could be heard. Tenderness was present in the left lower abdominal quadrant and on pelvic examination a small mass was found in the left adnexal region. The pulse was 86, respiratory rate 30, temperature 98° and weight 132 pounds. Blood pressures taken on 3 different occasions were: 108/90, 110/90 and 112/96.

*Roentgen Ray Study of the Chest* (Drs. F. B. Stephenson and K. D. A. Allen). The fluoroscopic examination revealed a bulging in the region of the pulmonary artery in which pulsations corresponded with ventricular systole; the excursion of both diaphragms was good. The roentgenograms of the chest showed a marked enlargement of the pulmonic arch, enlargement of the right ventricle and right auricle, and extensive fibrosis in the hilar regions and bronchial system. A comparison of the heart shadows in systole and diastole revealed increased width of the right heart in all phases and a failure of the heart to exhibit a normal range of change between diastole and systole, the right side of the heart showing only about half as much change as the left side when radiated in the two phases (Figs. 1 and 2*).

The electrocardiographic tracing showed the changes peculiar to right ventricular preponderance.

The average vital capacity was 2650 cc., and tidal air 700 cc. (Narragansett Wet Spirometer). This vital capacity was within normal limits for this patient but the tidal air was considerably above normal.

Nothing abnormal was found in the urine.

A fractional gastric analysis gave results within normal limits. A barium Roentgen ray series revealed no gastro-intestinal abnormalities save a spastic colon.

Blood chemistry studies gave normal findings as to dextrose, total nonprotein nitrogen and urea nitrogen. The bleeding and coagulation times were normal. The globulin and albumin respectively were 3 and 5.2 gm. per 100 cc. of serum. The blood serum osmotic pressure was 360. These determinations were all within normal limits. The hemocytologic findings are incorporated in Table 1. An increased level of hemoglobin and a moderate polycythemia were found.

*Clinical Course and Subsequent Observations.* During the first 7 days' observation this patient consumed 34 ounces of salt. She refused to go for more than 4 days without salt. Between the dates of December 12, 1932, and January 20, 1933, she was given 2 gm. of phenylhydrazin hydrochlorid which resulted in no alteration of the blood findings. On January 23, a small hemorrhoid was removed following which the patient hemorrhaged for 1 week, the red count dropping to 5,650,000 by January 31. On February 3 she entered the Colorado General Hospital where ad-

* The measurements noted are according to the careful work of Levene and Reid.[1]

ditional blood studies were made by Drs. E. R. Mugrage and R. H. Hill. Hemoglobin determinations from the same specimen of blood were made and the grams per 100 cc. of blood with each method used were as follows: 18.58, Van Slyke; 18.81, Wong; 19.50, Osgood-Haskins. The red count on this day was 6,265,000. The Kahn, Müller, Wassermann and Hinton tests for syphilis were all negative. Blood volume studies by the use of intravenous brilliant vital red were made. The results compared with the theoretical normals are as follows:

| | Patient. | Normal. |
|---|---|---|
| Plasma volume | 2669 cc. | 2969 cc. |
| Whole blood volume | 6221 cc. | 4640 cc. |
| Plasma volume per kg. | 46 cc. | 51 cc. |
| Whole blood volume per kg. | 107 cc. | 80 cc. |
| Plasma volume, % | 42.9 | 64 |
| Cell volume, % | 57.1 | 36 |

The red count on this day was 6,930,000.

On March 31 the patient returned to her home in Columbus where she reported for observation on April 6, 1933.

After her return to near sea level it was found that the red count decreased appreciably (Table 1). The Wassermann and Kahn tests were again found to be negative. Hemolysis began at a salt equivalent concentration of 0.430 and was complete at 0.267 (Wiseman technique[2]) showing increased erythrocyte resistance. The following additional data were obtained on the dates indicated.

| Date. | 4/6. | 4/12. | 4/18. | Comparison with normal. |
|---|---|---|---|---|
| Cell volume, % | 58 | 59 | 58 | High |
| Mean corpuscular volume | 92 | 120 | 118 | Normal to high |
| Mean corpuscular hemoglobin | 22 | 28 | 32 | Low to normal |
| Mean corpuscular hemoglobin concentration | 24 | 22 | 27 | Low |
| Sedimentation rate | 10 | 0 | 2 | Normal |
| Icteric index | 10 | 15 | 15 | High |

The basal metabolic rate was +5.

Studies directed toward the investigation of the abnormal salt intake were of considerable interest. Dr. S. Renshaw, in a careful study of her gustatory stimulus limens for sodium chlorid (that concentration of salt barely appreciable to taste), found her salt threshold to be strikingly low compared to "normal" individuals. Space does not permit the elaboration of the technical details necessary to make accurately such an observation. Briefly, the threshold for a given substance (sodium chlorid in this case) at a given temperature is determined by a method of linear interpolation after plotting the percentage of positive judgments against the corresponding solution strengths. A judgment is considered positive when the subject is able to differentiate between distilled water and the test solution. Table 2 gives the percentage of positive judgments made by our patient for various concentrations of sodium chlorid at temperatures ranging from 3° to 47° C. The figures at the bottom of the table are the values of the thresholds at these temperatures and are interpreted as fractions of a 1% solution by weight. In order to give some notion of the patient's sensitivity to the taste of salt, Fig. 3 compares her thresholds with those of individuals who were normal with respect to taste and salt intake.

Table 3 contains data relating to the daily fluid intake, urinary output, salt intake, urinary chlorid and blood chlorid. Data taken when the patient was allowed to ingest sodium chlorid in any amount is compared with that taken when no salt was permitted (Fig. 4).

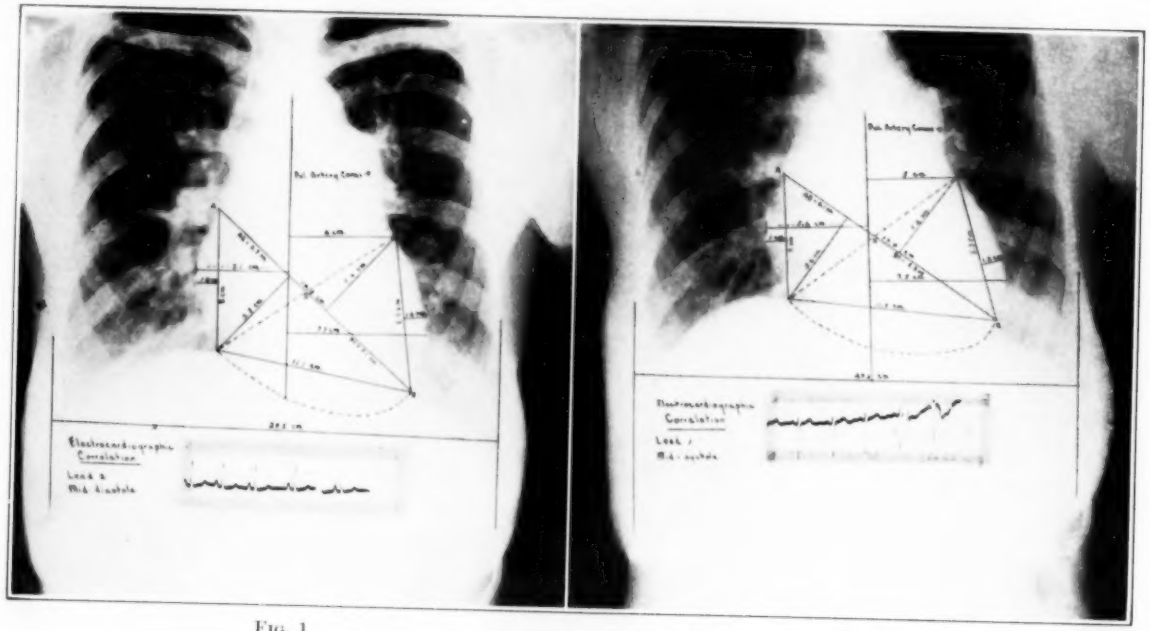

FIG. 1 FIG. 2

FIGS. 1 and 2.—Roentgenograms of the heart in diastole and systole.

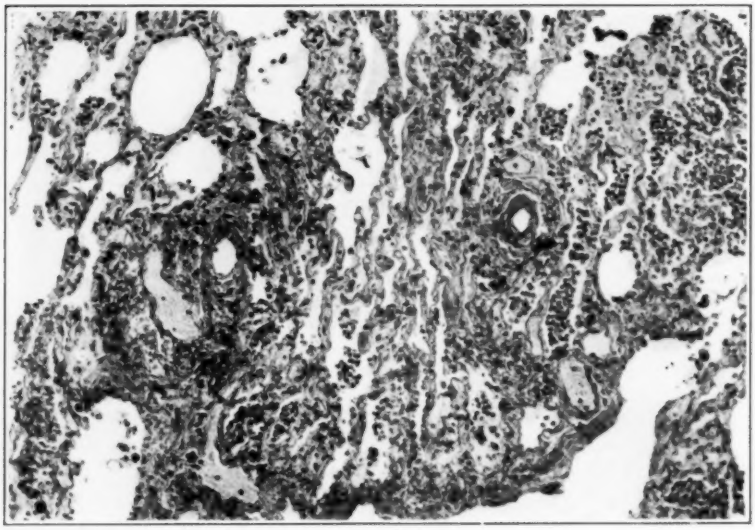

FIG. 6

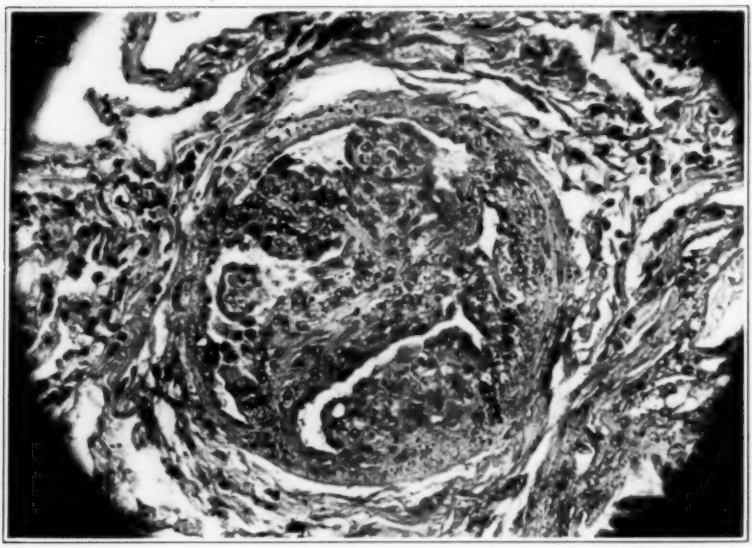

FIG. 7

FIGS. 6 and 7.—Showing vascular lesions with thickening of the vessel walls and narrowing of the lumina. Fig 7 shows an organizing thrombus within the vessel lumen.

TABLE 1.—SUMMARY OF HEMOCYTOLOGIC DATA AND FACTORS WHICH MIGHT BE EXPECTED TO INFLUENCE THE BLOOD PICTURE.

| Date. | Hgb. gm. per 100 cc. | R. B. C., millions per c.mm. | Retic., %. | W. B. C., thousands per c.mm. | P. M. N., %. | P. M. E., %. | P. M. B., %. | Lymph., %. | Monov., %. | Platelets thousands per c.mm. | Miscellaneous. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dec. 12, 1932 | 17.6 | 7.48 | ... | 9.1 | 73 | 2 | .. | 22 | 3 | ... | Initial reading, Denver. 2 gm. phenylhydrazin Dec. 12, 1932 to Jan. 20, 1933. |
| Jan. 23, 1933 | 17.6 | 7.46 | ... | 7.8 | 65 | 4 | 1 | 24 | 6 | ... | Hemorrhoidectomy. Anal hemorrhage for 1 week. |
| Jan. 31 | 15.0 | 5.65 | ... | 10.6 | 81 | 2 | .. | 17 | | | |
| Feb. 3 | 16.9 | 6.26 | ... | .... | .. | .. | .. | .. | .. | ... | Hemoglobin study. |
| Feb. 17 | 17.6 | 6.1 | ... | 13.2 | 80 | 2 | .. | 18 | .. | ... | Acute respiratory infection. |
| Feb. 23 | 20.4 | 6.93 | ... | 6.55 | 75 | .. | .. | 17 | 8 | ... | Blood volume study. |
| Mar. 28 | 17.6 | 7.17 | ... | .... | .. | .. | .. | .. | .. | ... | From Denver to Columbus. |
| April 6 | 14.0 | 6.3 | ... | 8.4 | 60 | 7 | 1 | 26 | 6 | ... | Initial reading, Columbus. |
| April 12 | 13.5 | 4.87 | 1.8 | 7.5 | 87 | 1 | .. | 29 | 13 | | |
| April 18 | 16.0 | 4.9 | 0.6 | 4.9 | 54 | 11 | 1 | 22 | 12 | 210 | |
| April 19 | 15.3 | 5.66 | ... | 6.3 | 61 | 3 | 3 | 31 | 2 | 100 | |
| April 20 | 14.0 | 5.75 | 0.2 | 5.05 | 56 | 1 | 1 | 28 | 14 | 80 | |
| May 12 | 14.0 | 5.35 | 0.8 | 7.25 | 66 | 5 | 2 | 18 | 8 | ... | 1 myelocyte. |
| June 9 | 15.3 | 6.12 | 3.4 | 6.8 | 78 | 4 | .. | 12 | 6 | ... | Day of operation. |

TABLE 2.—PERCENTAGES OF POSITIVE JUDGMENTS ON TASTE OF NaCl SOLUTIONS, WITH THRESHOLDS AT VARIOUS TEMPERATURES.

| Dates in May. | 10th. | 12th. | 5th. | 8th. | 16th. | 17th. | 11th. | 4th. | 19th. | 22d. | 23d. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sol. temp., °C. | 3 | 9 | 18 | 23 | 33 | 35 | 37 | 37 | 42 | 42 | 47 |
| % NaCl | | | | | | | | | | | |
| .070 | | 0 | | 0 | | | | | | | |
| .075 | | | 0 | 10 | | | | | | | |
| .080 | | 20 | 6 | 35 | 36 | | | | | | |
| .085 | | | 20 | | | | | | | | |
| .090 | 20 | 26 | 33 | | 44 | | | | | 5 | 0 |
| .095 | | | | 55 | | | | | | | |
| .100 | 35 | 55 | 53 | | 84 | 0 | | | 48 | 40 | 10 |
| .105 | | | | 75 | | | | | | | |
| .110 | 55 | 66.6 | 60 | | 80 | 10 | | | 72 | 70 | 55 |
| .115 | | | | 94 | | | | | | | |
| .120 | 55 | 86.6 | | | 76 | 15 | | | 75 | 80 | 80 |
| .125 | | | | 100 | | | | | | | |
| .130 | 85 | 93.3 | | | 65 | 55 | | | 94 | 85 | 75 |
| .135 | | | | | | | | | | | |
| .140 | | | | | 70 | 65 | | | | 100 | 70 |
| .145 | | | | | | | | | | | |
| .150 | | | | | | 90 | 15 | 0 | | | |
| 160 | | | | | | 100 | 35 | 26.6 | | | |
| 170 | | | | | | | 45 | 26.6 | | | |
| 180 | | | | | | | 65 | 33.3 | | | |
| 190 | | | | | | | 80 | 86.5 | | | |
| 200 | | | | | | | 85 | 73.0 | | | |
| 210 | | | | | | | 100 | | | | |
| Threshholds | .1075 | .098 | .098 | .0925 | .0915 | .12875 | .1725 | .1832 | .1008 | .1033 | .109 |

NOTE: Oral temperature was taken on each day and varied from 96.8 to 98.6° F.

When the patient took as much salt as she desired, it will be noted that the fluid intake and output averaged slightly higher than normal, that the urinary salt output although high was far below the salt intake and that

the whole blood and plasma chlorids were within normal limits. When salt was deleted from the diet the fluid intake and output became moderately diminished, the urinary salt output became less and both the whole blood and plasma chlorids showed a sharp and marked increase.

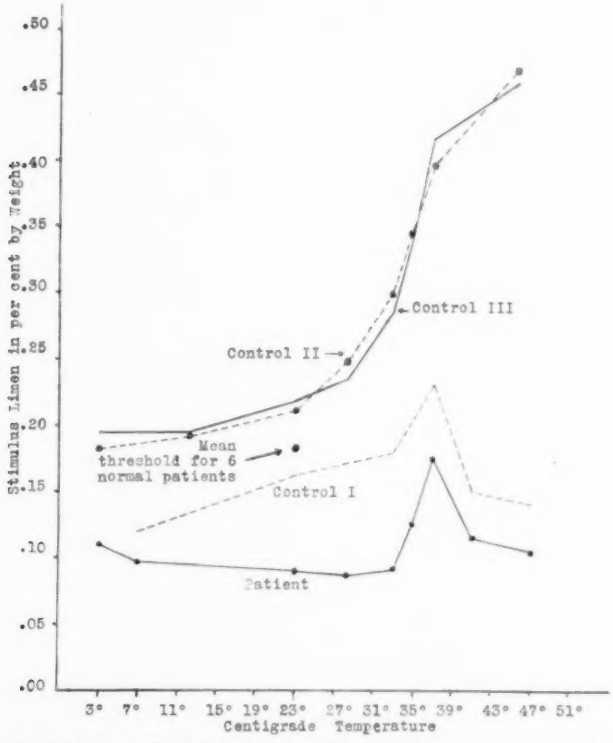


FIG. 3.—The influence of solution temperature on the stimulus limens for sodium chlorid.

TABLE 3.—CONSECUTIVE DAILY COMPARISONS OF FLUID INTAKE AND OUTPUT, SALT INTAKE, URINARY CHLORID AND BLOOD CHLORID.

| Date. | Intake, water. | Total urine. | Intake, salt, gm. | Urinary chlorid, gm. | Urinary chlorid, % | Blood chlorid, mg. per 100 cc. | |
|---|---|---|---|---|---|---|---|
| | | | | | | Whole blood. | Blood plasma. |
| April 21 | 2740 | 3200 | 90 | 22.88 | 0.71 | 495 | 559 |
| April 22 | 2110 | 1250 | 30 | 21.93 | 1.73 | 478 | 577 |
| April 23 | 2090 | 2000 | 135 | 22.6 | 1.13 | 478 | 643 |
| April 24 | 2490 | 1900 | 30 | 11.21 | 0.59 | | |
| May 9 | 1885 | 1250 | 60 | 9.75 | 0.78 | 495 | 627 |
| May 10 | 2160 | 1725 | 0 | 15.69 | 0.91 | 511 | 627 |
| May 11 | 1400 | 900 | 0 | 11.7 | 1.30 | 578 | 643 |
| May 12 | 1365 | 1100 | ... | 11.4 | 1.04 | | |
| May 30 | 1350 | 1900 | 120 | ..... | .... | 462 | 561 |
| May 31 | 1400 | 2750 | 120 | 21.25 | 0.78 | 426 | 610 |
| June 1 | 730 | 2300 | 60 | 14.94 | 0.65 | 500 | 618 |
| June 2 | 1100 | 3750 | 60 | 34.12 | 0.91 | 462 | 610 |
| June 3 | 1000 | 2600 | 0 | 20.28 | 0.78 | 432 | 594 |
| June 4 | 700 | 2200 | 0 | 8.58 | 0.39 | 561 | 643 |
| June 5 | 1080 | 500 | 0 | 2.60 | 0.52 | 561 | 660 |
| June 6 | 1400 | 1250 | ... | 6.5 | 0.52 | | |

On June 10, at the request of the patient, an exploratory operation on the pulmonary artery was performed by Dr. G. Curtis. The pulmonary artery was large. The heart was found to have rotated to the right in a clockwise direction throwing the pulmonary artery to the right and the aorta to the left and anteriorly. No gross obstruction was found and closure was made. During convalescence the patient developed bronchopneumonia from which she died on June 12, 1933.

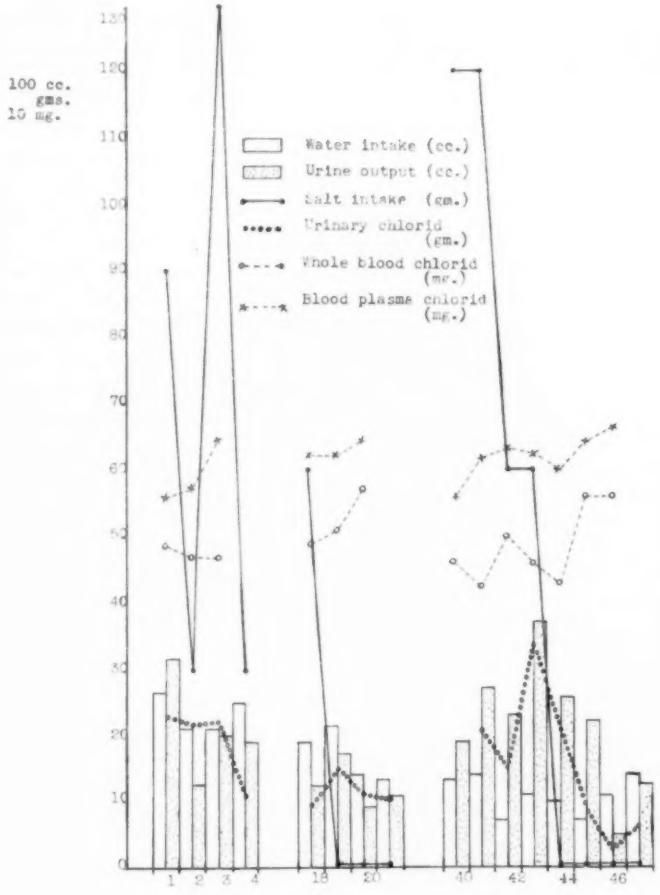


FIG. 4

*Partial Autopsy* (Dr. E. Scott). The heart weighed 330 gm. The right ventricle was prominent and on palpation was firmer than normal. The subpericardial fat and coronary arteries did not appear abnormal. The pulmonary artery was dilated, measuring 30 by 38 mm. and its walls were somewhat thickened. The aorta measured 22 by 24 mm. The tricuspid valve (10 cm. in circumference) showed slight diffuse thickening of the cusps but was competent. The pulmonary valves were normal (7 cm.); the mitral valve (7 cm.) was competent. The cusps were similar to those

of the tricuspid valve. The right ventricular wall measured 14 mm. in thickness; the left at the base of the papillary muscle, 12 mm. The aortic valves were normal (Fig. 5.)

Microscopic Findings. *Aorta.* A moderate degree of atheromatosis was found in the subintimal coat, the media appeared normal save for very slight infiltration of the outer margin and the adventitial coat contained a few more lymphocytic and monocytic cells than might be termed entirely normal. The changes were not regarded as sufficient to warrant a diagnosis of luetic aortitis.

*The pulmonary artery* was slightly thickened and fibrotic. The median layer was normal. A slight cellular infiltration of the adventitia was noted similar to that found in the aorta.

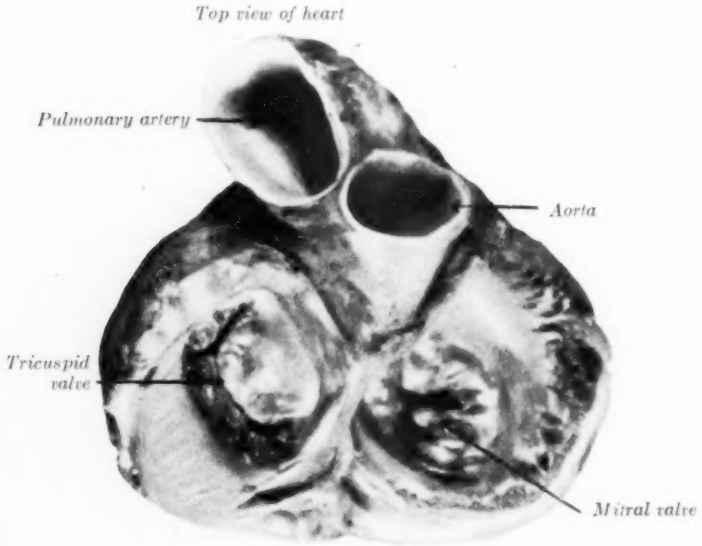


Fig. 5

*Spleen.* Moderate thickening of the capsule, some increase in stroma, rather diffuse increase in fibroblasts, a diminution in the pulp substance and some destruction of Malpighian corpuscles. The bloodvessels were generally thickened, chiefly due to adventitial fibrosis. In some of the smaller branches of the arterioles of the Malpighian bodies, there was some hyalin change involving the subintimal and median coats.

*Liver.* There was slight swelling of the liver cells. The interlobular branches of the hepatic artery were thickened due to adventitial fibrosis. The interlobular fibrous tissue in general was slightly increased.

*Lungs.* Microscopic changes characteristic of bronchopneumonia were found. Sections from near the hili revealed definite evidence of sclerosis and thickening of the branches of the pulmonary artery. The sclerosis was characterized by a thickening of the adventitial coat. These changes were conspicuous in both the large and median sized branches of the artery. In the smaller arterial divisions there was a proliferation on the part of the media which appeared to account entirely for the vessel thickening. In the precapillary vessels in many instances there appeared to be an endar-

teritis with almost complete occlusion of the vessel lumen. Occasionally changes which appeared to be those of thrombosis were found and in one vessel the resemblance to an organized thrombus with canalization was suggested (Figs. 6 and 7).

**Discussion.** In 1929, Moschcowitz's[3] excellent review of the causes and dynamics of pulmonary hypertension explained the clinical features in the light of physiologic compensation. Given the existence of hypertension in the lesser circulation, this author relates the sequence of events as follows: increased pulmonary diastolic pressure; overload to the right ventricle; right myocardial weakness with incomplete systolic discharge; overload to the right auricle; increased venous pressure with slowed capillary circulation. The anoxemia which results from incomplete oxygenation of the blood in the lungs and from increased deoxygenation of the blood in the tissues induces dyspnea, cyanosis and erythremia. The cyanosis is intensified by the polycythemia and by the venous stasis at the body surfaces. As the obstruction to the pulmonary circulation is prolonged and gradually increased in degree certain compensatory changes occur in the right heart (dilatation and hypertrophy) and in the pulmonary arteries (dilatation and sclerosis). The proliferative process in the pulmonary arteries adds in turn to the primary factors in the circulatory obstruction. As the result of this vicious cycle, tricuspid insufficiency must eventually develop with a still greater increase in venous pressure and in anoxemia. Venous stasis becomes more marked, swelling of the abdominal organs and ascites occur, dependent edema becomes pronounced and systemic diastolic pressure rises. The heart which is overburdened by increased venous return and increased peripheral resistance and which is undernourished because of decreased coronary flow and the marked anoxemia must eventually cease to function.

Clinically the course of pulmonary hypertension may be divided into two periods, the one before and the other after the onset of tricuspid incompetency. The first period may last for many years with the symptoms predominantly respiratory: in comparison the second period is much shorter with the symptoms predominantly cardiac.

Considered in the light of this general but brief discussion, our case fits into the picture as one presenting the clinical syndrome of obstruction to the lesser circulation prior to the onset of tricuspid incompetency. The clinical and laboratory findings important to the diagnosis, which for the most part have been previously reported in the literature, will be discussed but briefly save as they may show unusual deviation or seem to take on added significance.

The respiratory studies based upon the normals established by Dreyer and Hanson[4] revealed that the tidal air of our patient was greatly increased. We feel that this, as well as the dyspnea and

erythremia, represents an effort at compensation on the part of the respiratory mechanism and that such a finding is to be expected in the absence of accompanying pulmonary pathology.

That the increased red count noted in our patient represented a true erythremia was indicated by the increased whole blood volume. While an actual erythremia is usual in the syndrome of obstruction in the lesser circulation[5–9] the same observation has been made occasionally in patients living at high altitudes. In these cases, according to Monge,[10] the blood findings become normal on return to sea level. A normal individual with an adequate biologic mechanism of adaptation should show only temporary polycythemic changes on going to a high altitude. The fact that our patient's dyspnea became chronically aggravated in the Rocky Mountain region and the fact that her erythrocyte count and hemoglobin receded to normal shortly after her return to near sea level must indicate that her sojourn of more than a year in a mile-high altitude was a contributing cause of the erythremia. It seems reasonable that the lowered oxygen tension of high altitude would greatly aggravate the tendency toward polycythemia already present in an individual such as our patient with an obstruction in the pulmonary circulation.

It will be noted that the systolic and pulse pressures in our case were persistently low. It appeared to us that this might be of diagnostic significance in cases of obstruction to the lesser circulation for this reason: due to a narrowing of the pulmonary capillary bed the flow of blood to the left heart would be lessened which in turn would result in a low systolic and a small pulse pressure because of a lessened left ventricular discharge. Similar cases in which the blood pressures were reported[11–15] would seem to confirm our observation. Pund and Phinizy[16] particularly call attention to the low pulse pressure found in their case of pulmonary arteriosclerosis. It is also of significance that in the experimental work of Smith *et al.*,[17] which will be referred to later, it was noted that the systolic pressures became much lower in the animals which developed pulmonary arteriosclerosis.

The experimental work on the taste sensitivity of this patient for sodium chlorid is of considerable interest. Her salt intake was several hundred times that of each of 6 normal subjects. When the average taste threshold for sodium chlorid of these 6 persons was contrasted with that of our patient, it was found that her threshold was surprisingly low (0.185 as compared with 0.092). It would seem to us that an individual regularly taking such large quantities of salt would more logically be expected to manifest a decrease in taste sensitivity rather than an increase.

Whether or not the high salt intake noted represents a perversion of appetite or a metabolic or endocrine disturbance cannot be judged. Human cases of osmotic poisoning and even death from

the ingestion of sodium chlorid have been recorded. The literature contains many experimental studies involving a high sodium chlorid intake for relatively short periods of time but the prolongation of high salt intake noted in this patient is, so far as we have been able to determine, without parallel in the medical literature except for the reports of Thompson and McQuarrie[18] and McQuarrie.[19] These observers mention 4 cases of juvenile diabetes mellitus in which an abnormal craving for and ingestion of large quantities of sodium chlorid (as high as 80 gm. daily) was present. These patients presented a peripheral hypertension and a high fluid intake and output, all of which disappeared on removing the excess salt from the diet. When we compare the findings in our case we note, first, that our patient did not have diabetes; second, that she presented a peripheral hypotension; third, that her fluid intake and output did not closely parallel her salt intake; and fourth, that she appeared to be unable to delete the large amount of salt from her diet.

While the observations noted are of diagnostic and clinical interest, they contribute nothing toward an understanding of the etiology in this case. Moschcowitz[3] emphasizes that pulmonary arteriosclerosis (save the atheromatosis found in the aged) always indicates that hypertension of the lesser circulation is or has been present. With probably few exceptions (congenital heart disease with arteriovenous shunt and primary pulmonary hypertension) such hypertension is secondary to obstruction in the pulmonary circuit, which, if sufficiently prolonged, results in sclerosis of the arteries. From the following discussion it will be apparent that no definite cause of hypertension, other than the arterial and arteriolar hyperplasia, is evident. Many possible causes, however, present themselves and we have chosen to discuss these possibilities in 3 groups: the first considers congenital abnormalities of the heart and pulmonary vessels; the second, extravascular conditions of the lungs; the third, primary defects occurring in the pulmonary arteries and arterioles themselves.

If the statement that cyanosis appeared at 3 weeks of age is to be depended upon, it is probable that this individual was born with an inadequate circulo-respiratory mechanism. At autopsy no congenital cardiac defects were found. It is conceivable that malposition of the heart such as was found in our case might have resulted in constriction of any of the great vessels of the hilar regions but no evidence of such constriction was found. The dilatation of the pulmonary artery and the sclerosis of the smaller arteries throughout both lungs indicate obstruction acting in or on the arterioles and capillary bed or the venous system. A congenital hyperplasia of the arteries and arterioles could fit into such a picture and has been considered as an etiologic possibility by Steinberg[20] and Sisto.[21] That congenital sclerosis of arteries may occur has

been shown by the observations of Kissane and Fidler.[22] These authors report 1 case of congenital sclerosis of the coronary arteries and they review many similar cases from the literature, many of which were apparently secondary to intrauterine fetal infections. Narrowing of the pulmonary veins in pulmonary arteriosclerosis has been observed (Wätjen[23]) but according to Ljungdall[24] this should be considered as secondary to the diminished inflow of blood and not as a cause of increased resistance. Consequently such cases would involve a primary congenital hyperplasia of the arteries and arterioles.

Aside from cyanosis, definite symptoms suggesting a cardio-respiratory condition did not manifest themselves until our patient was 4 years old. This suggests that events occurring or developing prior to the age of 4 might have served to accentuate a congenital cardio-respiratory condition or that the early observation of cyanosis was incorrect in which case such events might primarily account for the condition. The first of several attacks of pneumonia and the onset of an abnormal appetite for salt occurred before our patient reached the age of 4 years and should perhaps be considered in this regard.

The repeated attacks of pneumonia during early childhood may well have been associated with a chronic interstitial pneumonitis and have resulted in hypertension for a sufficient period to initiate arteriosclerotic changes. With the ultimate resolution of the infection, pulmonary arteriosclerosis and hypertension would have remained.

Since a prolonged high salt intake had been so prominent in our case, the possibility that this might result in pulmonary arteriosclerosis must be thought of. It has recently been shown (Smith *et al.*[17]) that in rats chronic pulmonary edema induced by the prolonged inhalation of oxygen can cause alveolar fibrosis and pulmonary arteriosclerosis. With continued exposure to oxygen the edema disappears but the arteriosclerosis and alveolar changes persist. Listing the experimental methods of inducing pulmonary edema, Wiggers[25] mentions the intravenous injection of saline solutions. One of us (W. D.) was able to induce fatal pulmonary edema in rabbits following the oral administration of large daily doses of salt over a period of from 1 to 6 weeks. No evidence, however, of pulmonary or peripheral arteriosclerosis could be found in these animals postmortem. A small series of young mice was likewise maintained upon a standard diet containing from 3 to 5% salt for as long as 6 months; microscopic examination of the lungs and other tissues revealed no evidence of arteriosclerosis. It has previously been noted that peripheral hypertension was present in the cases of high salt intake reported by Thompson and McQuarrie.[18,19] These observers also noted an elevation of the peripheral blood pressure in normal individuals who ingested a comparative

dosage of salt. Such investigations and observations, while not extensive, would seem to indicate the unlikelihood that a prolonged high salt intake could induce an independent hypertension in the lesser circulation.

Although the above etiologic possibilities may apply to certain cases, it is apparent that in our case the cause cannot be proven to be due to a congenital cardiac or vascular abnormality or to an extravascular pulmonary condition. Consequently the probability of a cause arising or existing primarily in the pulmonary arteries and arterioles themselves must be considered. But few carefully studied cases of primary pulmonary arteriosclerosis have been reported. Hare and Ross,[11] after a careful review of the literature before 1929, felt that only 23 cases justified such a designation. They added one more of their own. Excellent papers upon the subject have also been published by Steinberg,[20] Sisto,[21] Pund and Phinizy[16] and Ulrich.[26] It thus becomes evident that in the cases of primary pulmonary arteriosclerosis certain characteristics are apt to appear which are infrequent or absent in the secondary cases. The secondary sclerosis is most apt to occur (save in patients with congenital heart disease) after 40, while the primary condition is more prone to develop in younger individuals. Clubbing of the fingers is less likely to be present in the primary than in the secondary cases. If the condition is primary, the sclerosis is more or less confined to the small arteries and arterioles and the hypertrophy of the right heart is most marked. If the condition is secondary, the sclerosis is more apt to involve the large arteries and the hypertrophy of the right heart is less conspicuous. It is evident that in all these respects our case appears to be one of primary pulmonary arteriosclerosis.

Syphilis (as proven by characteristic histopathologic findings) is undoubtedly the most frequent cause of primary pulmonary arteriosclerosis. Our case showed no characteristic findings of syphilitic arteritis in sections of the lung, which, according to present standards, is sufficient to rule out such a diagnosis.

Sokoloff and Stewart[27] have reported a case in which, although a history of severe asthmatic paroxysms requiring frequent and large doses of adrenalin was present, an endocrine cause was considered. Unfortunately permission for an abdominal and cranial autopsy was refused by the relatives of our patient and no data regarding the adrenals or pituitary is available. It is possible that the high salt intake noted in our patient may have been a manifestation of some unusual malfunction of the adrenal or pituitary glands. There is this possibility but no clinical evidence of endocrinopathy was demonstrable.

Instances of apparent idiopathic pulmonary arteriosclerosis have been reported. Hare and Ross,[11] in 1929, gathered 7 such cases from the literature. One more has since been reported by Pund

and Phinizy[16] and 2 by Ulrich.[26] Two of the cases found in the literature by Hare and Ross and the case of Pund and Phinizy were luetics, but microscopic examination of the pulmonary vessels ruled out a syphilitic arteritis. Consequently these 3 cases may be included in the idiopathic group. It is interesting that these cases of unknown etiology are found in young adults; the average age of the above cases being 29 years and, if those with lues are excluded, 23.2 years. If age is significant, our patient would seem to fit in with this small group of idiopathic cases and we feel that, while several etiologic bases for the condition found in our patient have been presented for consideration, the proof for the underlying cause remains incomplete. Therefore, we prefer to classify our case as one of primary pulmonary arteriosclerosis of unknown etiology—at least until it can again be reviewed in the light of greater knowledge than we now possess.

**Summary.** The case herewith presented is that of a young female, aged 20, who since early childhood had manifested the signs and symptoms of obstruction in the lesser circulation. Autopsy revealed marked pulmonary arteriolar sclerosis, dilatation of the pulmonary artery and right ventricular hypertrophy.

During most of her life the patient had ingested abnormally large amounts of salt (as much as 3 pounds in 1 week). No cause for this abnormality could be found. It is of interest that her taste threshold for salt was much lower than the thresholds of persons who were normal in respect to salt desire and intake, that her fluid intake and output were not materially disturbed by variations in salt intake and that the osmotic pressure and the chemistry of the blood were not altered.

The case is discussed at length from the standpoint of possible causes of arteriosclerosis. Moschcowitz insists that, save with very few exceptions, pulmonary arteriosclerosis is the result of long-standing hypertension in the lesser circulation. Most such cases of hypertension are secondary to congenital abnormalities of the heart or pulmonary vessels or to extravascular or intravascular circulatory obstruction. In this patient we were unable to demonstrate any cause of obstruction or hypertension in the lesser circulation other than the arteriolar hyperplasia itself. Consequently we consider this case to be one of primary pulmonary arteriosclerosis and, since microscopic examination of the pulmonary tissue failed to reveal any evidence of luetic arteritis, we feel that it should be further classified as one of unknown etiology.

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## VARIATIONS IN SYSTOLIC BLOOD PRESSURE IN RENAL TUMOR: A STUDY OF 491 CASES.

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The kidney has always played a major rôle in any discussion of the cause of hypertension. There is justification for this because, in the majority of subjects with hypertension, the renal parenchyma is profoundly altered. Despite this fact and the volume of work which has been done to establish the cause of this alteration, an adequate explanation has not yet been found. Renal tumors have at various times been mentioned as a basis for hypertension,[10,11] and indeed an increased arterial tension has been cited as evidence valuable for clinical identification of a renal tumor.[3]

The commonest tumor of the kidney, the so-called hypernephroma, derives its name from the close histologic relationship it bears to the suprarenal cortex. Hypertension was noted by some observers

in persons who had hypernephroma, and because of the resemblance of the tumor to suprarenal tissue it was postulated that the hypertension was caused by an excessive production by the tissue of the tumor of a pressor substance analogous to that produced by the normal suprarenal gland. There are numerous reports[5,8,9] of marked clinical hypertension among patients who were later shown to have suprarenal tumors, and in some cases relief of the hypertension was afforded by removal of the tumor. Not all these tumors were of like histologic structure. Some appeared to be derived from the cortical tissue and others from the medullary tissue of the suprarenal gland.

Various types of tumors have been observed in cases of paroxysmal hypertension. C. H. Mayo[7] reported one of the first verified cases. On exploration he found an oval retroperitoneal mass, 6 by 4 cm., situated behind the tail of the pancreas on the mesial side of the left kidney and impinging against the upper pole. The tumor was removed. It appeared to be composed of nerve tissue containing ganglion-like cells, but because of the absence of marked differentiation this analogy was in no way complete. After fixation in formaldehyde the grayish color of the tumor changed to an orange-yellow, giving the mass the appearance of a suprarenal cortical adenoma, but the characteristic differentiated cells in glandular arrangement were lacking. A diagnosis was made of a malignant retroperitoneal blastoma. The attacks of paroxysmal hypertension ceased after removal of the tumor. Since this time reports of 8 similar cases, the tumors being identified at surgical exploration, have appeared in the literature.

Although authentic instances are few in number, it is nevertheless generally considered that a hypernephroma of renal origin usually causes an elevation in the blood pressure. Volhard observed 2 cases of hypernephroma in which occurred the diffuse clinical picture of hypertensive nephritis with albuminuria and a rise in blood pressure, both phenomena disappearing as soon as the tumor was removed. Voelcker and Boeminghaus stated that a sharp rise in blood pressure was noticed by many observers among patients suffering from renal tumors, and that since this phenomenon is connected with an increased production of epinephrin in Grawitz tumors (hypernephromas), so an extraordinarily high blood pressure supervening in the case of a pre-existing renal tumor can give an indication of the histopathologic nature of the tumor. Ljunggren[6] cited Voelcker's views and analogous ones of Blum but was unable to find epinephrin in the renal tumors which he analyzed. In 12 cases of hypernephroma in which adequate studies of blood pressure had been made he found no decrease in the arterial tension after surgical removal of the tumor. He therefore concluded that hypernephromas do not obviously produce a substance which increases the blood pressure.

Federoff used Ehrmann's enucleated frog's-eye test for epinephrin to demonstrate an excess of an epinephrin-like substance in a hypernephroma. He was unable to find a similar substance in control renal tissue and cited this as an aid in establishing the diagnosis of hypernephroma. Greer and Wells,[4] in 1909, and Brooks,[1] in 1911, were unsuccessful in attempts to confirm Federoff's work. These workers searched for an epinephrin-like substance, by the intravenous injection of tissue extract into dogs, and watched for a rise in blood pressure by Ehrmann's[2] enucleated frog's eye test and by colorimetric means. Brooks found no epinephrin-like substance in specimens of blood from 3 patients suffering respectively from a malignant hypernephroma, metastatic lesions from a hypernephroma-like suprarenal tumor, and 2 typical renal hypernephromas. This is as one would expect because a hypernephroma resembles suprarenal cortex, which portion of the suprarenal gland plays no part in the production of epinephrin.

It was in the hope that aid in clarifying this situation would be obtained by an adequate analysis of the blood pressures of persons suffering from renal tumors that the present study was undertaken, particularly since it seemed to us that heretofore any statements of the relation of renal tumors to systolic blood pressure were made on a conviction reached by a study of isolated cases.

The material used for study consisted of the records of patients with renal tumors who were admitted to the clinic between 1912 and 1934. We considered a total of 491 cases of all types, in which 340 (69%), of the patients were males and 151 (31%) females. In 459 cases there was a record of the pre-operative systolic blood pressure. Since the only readings of blood pressure noted were often those taken when the patient was first seen at the clinic, for the sake of uniformity we have used only these primary readings. Though the readings were taken by different persons, and though estimations of blood pressure taken with the patient under the considerable nervous strain of the first visit are admittedly higher than those which must be considered normal for each patient, we feel that the error so introduced will be negligible and is certainly unavoidable when records over such a long period must be relied on.

We have arbitrarily divided our renal tumors into two groups: (1) hypernephromas, and (2) tumors of other types, which included papillary squamous-cell epitheliomas, sarcomas, hemangio-endotheliomas, and so forth. In 335 cases in which the blood pressure was recorded pre-operatively, a pathologic diagnosis of renal adenocarcinoma of the hypernephroma type was made, 247 of the patients being males, 88 females.

Considering the males with hypernephroma (Table 1), we noted that they range in age from 10 to 80 years, the majority (72%) being between 45 and 65. Of this group 60% had a blood pressure between 100 and 139 mm. of mercury (which we are considering as a normal

range for our present study), 0.8% had definite hypotension, that is, a systolic pressure less than 100, and 39.2% had hypertension, that is, a systolic pressure of 140 or more. When we plotted the actual readings of blood pressure and superimposed the arithmetic mean of the different age groups in the form of a curve (Fig. 1) we found that this closely approached the curve obtained by plotting the arithmetic mean for the different age groups obtained by a similar analysis of a large series of normal males, being perhaps slightly, but hardly significantly elevated above the normal value.

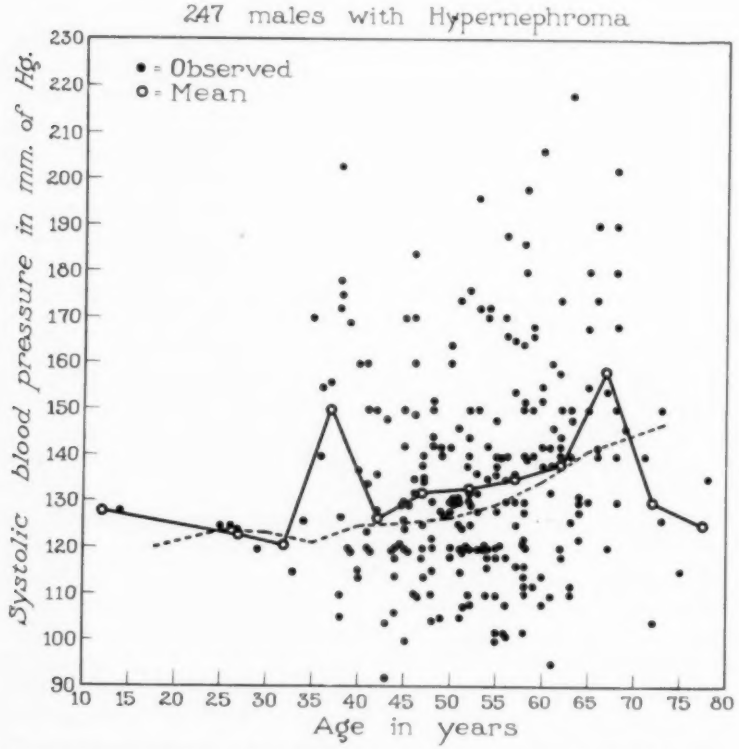


FIG. 1.—The continuous line is the curve of the mean systolic blood pressures. The broken line is a control curve representing the mean systolic blood pressures of normal males.

The postoperative blood pressure was recorded for 81 of the males who had hypernephroma (Table 2). The interval elapsing between operation and the time the postoperative reading was obtained varied from a few days to several years in some instances. Of these 81 males, 63.1% had a systolic pressure between 100 and 139, 1.2% had a systolic pressure less than 100, and 34.7% had a reading of 140 or more. These incidences are almost identical with those in similar

groups prior to removal of the tumor. When these readings were plotted (Fig. 2) and the arithmetic means superimposed in the form of a curve, the mean values were again found very closely to approximate the mean for normal males. In short, our observations derived from an analysis of the pre-operative and postoperative records of the blood pressure of males with hypernephroma would lead us to suspect that a hypernephroma does not cause a consistent elevation

TABLE 1.—SYSTOLIC BLOOD PRESSURES OF 247 MALES WITH HYPERNEPHROMA.

| Systolic blood pressure in mm. of mercury. | Age, years. | | | | | | | | | | | | | | Total. | Per cent. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 10 to 14 | 15 to 19 | 20 to 24 | 25 to 29 | 30 to 34 | 35 to 39 | 40 to 44 | 45 to 49 | 50 to 54 | 55 to 59 | 60 to 64 | 65 to 69 | 70 to 74 | 75 to 79 | | |
| 90 to 99 | ... | ... | ... | ... | ... | ... | 1 | ... | ... | ... | 1 | ... | ... | ... | 2 | 0.8 |
| 100 to 109 | ... | ... | ... | ... | ... | 1 | 2 | 3 | 3 | 6 | 1 | ... | 1 | ... | 17 | 6.9 |
| 110 to 119 | ... | ... | ... | ... | 1 | 1 | 4 | 6 | 6 | 9 | 6 | ... | 1 | 1 | 35 | 14.2 |
| 120 to 129 | 1 | ... | ... | 4 | 1 | 3 | 8 | 10 | 14 | 8 | 4 | 1 | 1 | ... | 55 | 22.3 |
| 130 to 139 | ... | ... | ... | ... | ... | 1 | 3 | 9 | 12 | 7 | 5 | 2 | 1 | 1 | 41 | 16.6 |
| 140 to 149 | ... | ... | ... | ... | ... | 2 | 1 | 7 | 5 | 7 | 9 | 4 | 1 | ... | 36 | 14.6 |
| 150 to 159 | ... | ... | ... | ... | ... | 1 | 2 | 3 | 2 | 4 | 5 | 4 | ... | ... | 21 | 8.5 |
| 160 to 169 | ... | ... | ... | ... | ... | 4 | 2 | 1 | 2 | 5 | 1 | 2 | ... | ... | 17 | 6.8 |
| 170 to 179 | ... | ... | ... | ... | ... | ... | ... | 2 | 5 | 1 | 1 | 1 | ... | ... | 10 | 4.1 |
| 180 to 189 | ... | ... | ... | ... | ... | ... | ... | 1 | ... | 3 | ... | 2 | ... | ... | 6 | 2.4 |
| 190 to 199 | ... | ... | ... | ... | ... | ... | ... | ... | ... | 1 | ... | 2 | ... | ... | 3 | 1.2 |
| 200 to 209 | ... | ... | ... | ... | ... | 1 | ... | ... | ... | ... | 1 | 1 | ... | ... | 3 | 1.2 |
| 210 to 219 | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | 1 | ... | ... | ... | 1 | 0.4 |
| Average pressure | 128 | ... | ... | 124 | 121 | 150 | 127 | 132 | 133 | 135 | 139 | 158 | 130 | 125 | 136 | |
| Total patients | 1 | ... | ... | 4 | 2 | 14 | 23 | 42 | 49 | 51 | 35 | 19 | 5 | 2 | 247 | |

TABLE 2.—SYSTOLIC BLOOD PRESSURES OF 81 MALES AFTER NEPHRECTOMY FOR HYPERNEPHROMA.

| Systolic blood pressure in mm. of mercury. | Age, years. | | | | | | | | | Total. | Per cent. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 25 to 29 | 30 to 34 | 35 to 39 | 40 to 44 | 45 to 49 | 50 to 54 | 55 to 59 | 60 to 64 | 65 to 69 | | |
| 90 to 99 | ... | ... | ... | 1 | ... | ... | ... | ... | ... | 1 | 1.2 |
| 100 to 109 | ... | 1 | 1 | 1 | 1 | 1 | 2 | ... | ... | 7 | 8.7 |
| 110 to 119 | 2 | ... | ... | 3 | 3 | 2 | 5 | 3 | ... | 18 | 22.2 |
| 120 to 129 | ... | ... | 1 | 3 | 3 | 5 | 3 | 2 | 1 | 18 | 22.2 |
| 130 to 139 | ... | ... | ... | ... | 3 | 3 | 1 | 1 | ... | 8 | 10.0 |
| 140 to 149 | ... | ... | ... | 1 | 3 | 2 | 1 | 2 | 1 | 10 | 12.3 |
| 150 to 159 | ... | ... | ... | ... | ... | 1 | 2 | ... | 2 | 5 | 6.2 |
| 160 to 169 | ... | ... | ... | ... | 1 | ... | ... | 2 | ... | 3 | 3.7 |
| 170 to 179 | ... | ... | 1 | ... | 3 | 1 | ... | ... | 2 | 7 | 8.7 |
| 180 to 189 | ... | ... | ... | ... | ... | ... | 1 | ... | ... | 1 | 1.2 |
| 190 to 199 | ... | ... | ... | ... | ... | ... | 1 | ... | ... | 1 | 1.2 |
| 200 to 209 | | | | | | | | | | | |
| 210 to 219 | ... | ... | ... | ... | ... | 1 | ... | 1 | ... | 2 | 2.4 |
| Average pressure | 111 | 106 | 130 | 115 | 135 | 135 | 131 | 140 | 151 | 133 | |
| Total patients | 2 | 1 | 3 | 9 | 17 | 16 | 16 | 11 | 6 | 81 | |

of blood pressure, and we did not verify Volhard's observation that a fall in arterial tension consistently followed surgical removal of a renal hypernephroma.

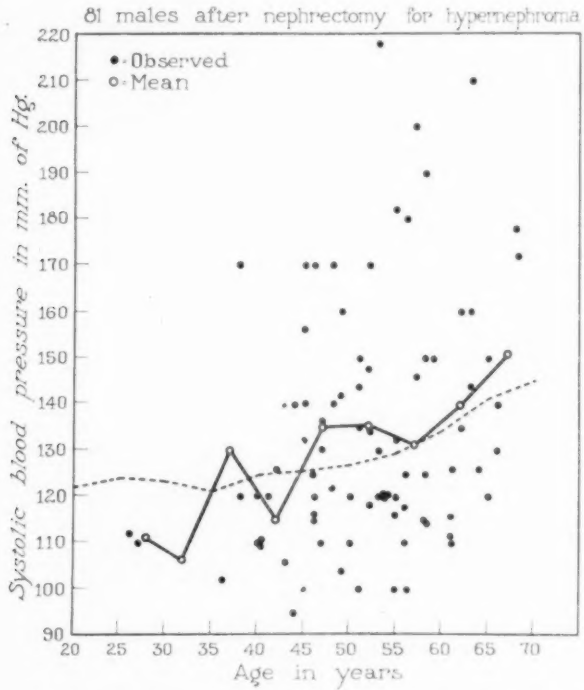


FIG. 2.—The continuous line is the curve of the mean systolic blood pressures. The broken line is a control curve representing the mean systolic blood pressures of normal males.

There were 88 females with hypernephromas for whom there was an available pre-operative record of the blood pressure (Table 3). Sixty-two (70.4%) ranged in age from 45 to 65. Of the eighty-eight, 45.3% had a systolic blood pressure between 100 and 139, 1.2% had a systolic blood pressure less than 100 and 53.5% had a reading of 140 or more. We plotted each reading and superimposed a curve representing the arithmetic mean for the various age groups (Fig. 3). Here again the mean value is found to approximate closely that obtained by a similar analysis of normal females, although it is consistently slightly higher. The postoperative blood pressure was recorded in 17 of these cases. Eight of the patients (47%) had a postoperative reading between 100 and 139, and 53% had a reading of 140 or more. That the incidence for the different ranges of blood pressure was practically unaltered by removal of the tumor seems to us to be significant.

TABLE 3.—SYSTOLIC BLOOD PRESSURES OF 88 FEMALES WITH HYPERNEPHROMA.

| Systolic blood pressure in mm. of mercury. | Age, years. | | | | | | | | | | | | | | Total. | Per cent. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 10 to 14 | 15 to 19 | 20 to 24 | 25 to 29 | 30 to 34 | 35 to 39 | 40 to 44 | 45 to 49 | 50 to 54 | 55 to 59 | 60 to 64 | 65 to 69 | 70 to 74 | 75 to 79 | | |
| 90 to 99 | ... | ... | ... | ... | ... | ... | ... | ... | 1 | ... | ... | ... | ... | ... | 1 | 1.2 |
| 100 to 109 | ... | ... | ... | ... | ... | ... | 1 | ... | ... | ... | 1 | ... | ... | ... | 2 | 2.2 |
| 110 to 119 | ... | ... | ... | ... | ... | 2 | ... | ... | 2 | 4 | 2 | 1 | ... | ... | 11 | 12.5 |
| 120 to 129 | ... | ... | ... | ... | 1 | 1 | 3 | 2 | 2 | 4 | 1 | ... | ... | ... | 13 | 14.7 |
| 130 to 139 | ... | ... | ... | 1 | 2 | 1 | 1 | 3 | 2 | 1 | 1 | 1 | 1 | ... | 14 | 15.9 |
| 140 to 149 | ... | ... | ... | ... | 1 | ... | 1 | 1 | 6 | 1 | 2 | 1 | 1 | ... | 14 | 15.9 |
| 150 to 159 | ... | ... | ... | ... | ... | ... | 1 | 1 | 5 | 2 | ... | 1 | ... | ... | 10 | 11.3 |
| 160 to 169 | ... | ... | 1 | ... | ... | ... | ... | ... | 1 | 3 | ... | 1 | ... | ... | 6 | 6.8 |
| 170 to 179 | ... | ... | ... | ... | ... | 1 | ... | ... | 1 | 4 | 1 | 1 | ... | ... | 8 | 9.1 |
| 180 to 189 | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | 3 | ... | ... | ... | 3 | 3.4 |
| 190 to 199 | ... | ... | ... | ... | ... | ... | ... | ... | ... | 1 | ... | ... | ... | ... | 1 | 1.2 |
| 200 to 209 | ... | ... | ... | ... | ... | ... | ... | ... | ... | 1 | ... | ... | ... | ... | 1 | 1.2 |
| 210 to 219 | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | 1 | ... | ... | ... | 1 | 1.2 |
| 220 to 229 | ... | ... | ... | ... | ... | ... | ... | ... | 1 | 1 | ... | ... | ... | ... | 2 | 2.2 |
| 230 to 239 | ... | ... | ... | ... | ... | ... | 1 | ... | ... | ... | ... | ... | ... | ... | 1 | 1.2 |
| Average pressure | ... | ... | 165 | 130 | 136 | 130 | 143 | 133 | 143 | 151 | 150 | 146 | 138 | ... | 145 | |
| Total patients | ... | ... | 1 | 1 | 3 | 5 | 8 | 7 | 21 | 22 | 12 | 6 | 2 | ... | 88 | |

TABLE 4.—SYSTOLIC BLOOD PRESSURES OF 76 MALES WITH RENAL TUMORS OTHER THAN HYPERNEPHROMA.

| Systolic blood pressure in mm. of mercury. | Age, years. | | | | | | | | | | Total. | Per cent. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 25 to 29 | 30 to 34 | 35 to 39 | 40 to 44 | 45 to 49 | 50 to 54 | 55 to 59 | 60 to 64 | 65 to 69 | 70 to 74 | | |
| 100 to 109 | ... | ... | ... | 1 | 3 | 4 | ... | ... | 2 | ... | 10 | 13.1 |
| 110 to 119 | ... | ... | 1 | 1 | 4 | 4 | ... | 1 | 1 | ... | 12 | 15.8 |
| 120 to 129 | 1 | ... | ... | 1 | 4 | 2 | ... | 2 | 1 | ... | 11 | 14.5 |
| 130 to 139 | 1 | ... | ... | 2 | 2 | 2 | ... | 1 | 4 | ... | 12 | 15.8 |
| 140 to 149 | ... | ... | ... | 2 | 3 | ... | 5 | 1 | 3 | ... | 14 | 18.4 |
| 150 to 159 | ... | 1 | ... | 1 | ... | 3 | ... | 3 | ... | ... | 8 | 10.6 |
| 160 to 169 | ... | ... | 1 | ... | ... | ... | 1 | 3 | 1 | 1 | 7 | 9.2 |
| 170 to 179 | | | | | | | | | | | | |
| 180 to 189 | ... | ... | ... | ... | ... | ... | 1 | ... | ... | ... | 1 | 1.3 |
| 190 to 199 | ... | ... | ... | ... | ... | ... | ... | 1 | ... | ... | 1 | 1.3 |
| Average pressure | 125 | 150 | 140 | 129 | 122 | 122 | 150 | 147 | 132 | 160 | 132 | |
| Total patients | 2 | 1 | 2 | 8 | 16 | 15 | 7 | 12 | 12 | 1 | 76 | |

The mean pre-operative systolic blood pressure for the males with hypernephroma was 136, for the females 145. Though these values are admittedly elevated over those considered normal, if we are to consider that this is due to the pressor action of a substance secreted by the hypernephroma, we have no explanation why removal of the tumor does not consistently result in a lowering of the blood

pressure. That such a drop does not occur is evident from our analysis, and it is verified when we find that the mean postoperative value for the blood pressure of males and females who had hypernephroma is 133 and 144, respectively.

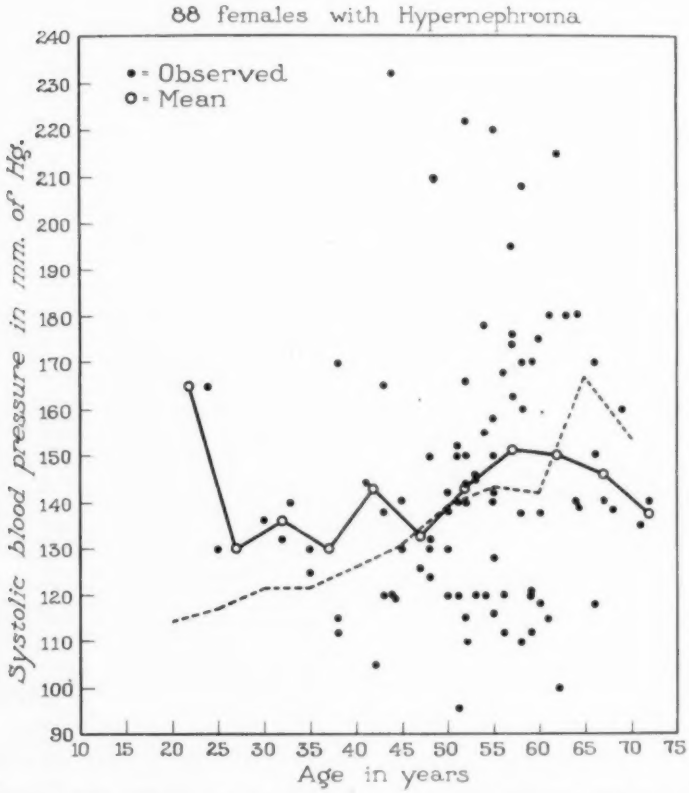


FIG. 3.—The continuous line is the curve of the mean systolic blood pressures. The broken line is a control curve representing the mean systolic blood pressures of normal females.

There were 76 males with renal tumors other than hypernephromas (Table 4), 59.2% having a systolic blood pressure between 100 and 139, and 40.8% a systolic blood pressure of 140 or more. This incidence is almost identical to that for like ranges of blood pressure among males with hypernephroma. The arithmetic mean for this group closely approximated the normal (Fig. 4). A postoperative record of the blood pressure was obtained in 24 cases; 66.7% had a reading between 100 and 139, 8.3% a reading less than 100, and 25% a reading of 140 or more.

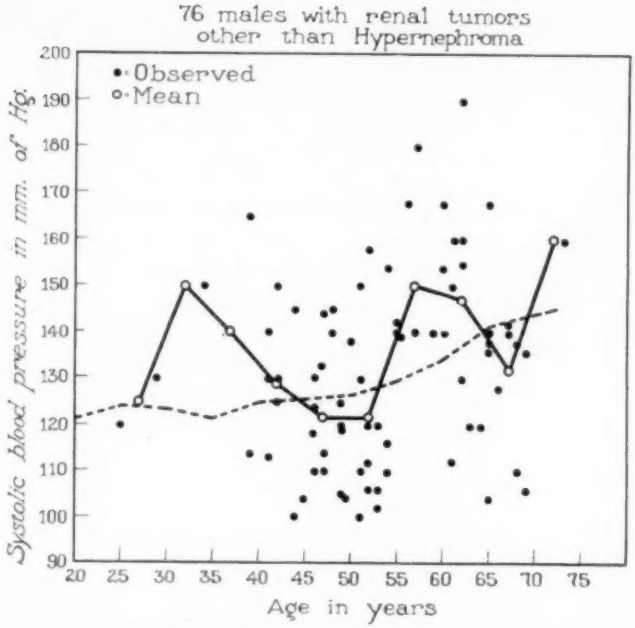


FIG. 4.—The continuous line is the curve of the mean systolic blood pressures. The broken line is a control curve representing the mean systolic blood pressures of normal males.

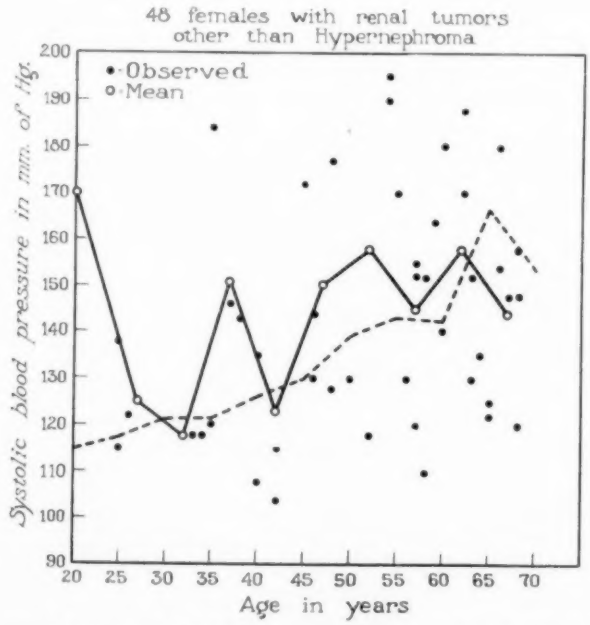


FIG. 5.—The continuous line is the curve of the mean systolic blood pressures. The broken line is a control curve representing the mean systolic blood pressures of normal females.

There were 48 females with renal tumors other than hypernephromas (Table 5), 45.8% of these having a systolic blood pressure between 100 and 139, and 54.2% one of 140 or more. It is to be noted that this percentage distribution is practically identical with that for the group of females with hypernephromas, and the arithmetic mean blood pressure closely approaches the normal value (Fig. 5). In 20 cases in which a postoperative record was made, 40% of the patients had a blood pressure between 100 and 139, 60% one of 140 or more.

TABLE 5.—SYSTOLIC BLOOD PRESSURES OF 48 FEMALES WITH RENAL TUMORS OTHER THAN HYPERNEPHROMA.

| Systolic blood pressure in mm. of mercury. | Age, years. | | | | | | | | | | | Total | Per cent. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 15 to 19 | 20 to 24 | 25 to 29 | 30 to 34 | 35 to 39 | 40 to 44 | 45 to 49 | 50 to 54 | 55 to 59 | 60 to 64 | 65 to 69 | | |
| 100 to 109 | ... | ... | ... | ... | ... | 2 | ... | ... | ... | ... | ... | 2 | 4.1 |
| 110 to 119 | ... | ... | 1 | 2 | ... | 1 | ... | 1 | 1 | ... | ... | 6 | 12.5 |
| 120 to 129 | ... | ... | 1 | ... | 1 | ... | 1 | ... | 1 | ... | 3 | 7 | 14.6 |
| 130 to 139 | ... | ... | 1 | ... | ... | 1 | 1 | 1 | 1 | 2 | ... | 7 | 14.6 |
| 140 to 149 | ... | ... | ... | ... | 2 | ... | 1 | ... | ... | ... | 2 | 5 | 10.5 |
| 150 to 159 | ... | ... | ... | ... | ... | 1 | ... | ... | 3 | 2 | 2 | 8 | 16.7 |
| 160 to 169 | 1 | ... | ... | ... | 1 | ... | ... | ... | 1 | ... | ... | 3 | 6.3 |
| 170 to 179 | ... | ... | ... | ... | ... | ... | 2 | ... | 1 | 1 | ... | 4 | 8.3 |
| 180 to 189 | ... | ... | ... | ... | 1 | ... | ... | ... | ... | 2 | 1 | 4 | 8.3 |
| 190 to 199 | ... | ... | ... | ... | ... | ... | ... | 2 | ... | ... | ... | 2 | 4.1 |
| Average pressure | 169 | ... | 125 | 118 | 151 | 123 | 150 | 158 | 145 | 158 | 144 | 145 | |
| Total patients | 1 | ... | 3 | 2 | 5 | 5 | 5 | 4 | 8 | 7 | 8 | 48 | |

In our series there were 6 cases of hypernephroma in which a definite involvement of the suprarenal glands was proved, and of these a marked hypertension was present in only 2 cases. In 3 of these 6 cases the tumor seemed to arise primarily in the suprarenal gland. One of the patients had practically a normal blood pressure with a reading of 142 systolic and 84 diastolic. One had hypertension of moderate degree with a blood pressure of 190 systolic and 100 diastolic. The third patient had marked hypertension, with retinal arteriosclerosis, retinal hemorrhage, cardiac enlargement, and a blood pressure of 232 systolic and 145 diastolic. There was no postoperative record in any of these 3 cases. There were 19 cases in which definite suprarenal involvement was not proved histologically, but it should be inferred because of the origin of the tumor in the upper pole of the kidney and its extension to involve the diaphragm. In this group of cases hypertension existed in 4 cases; an absolute hypotension with a systolic reading of 96 was present in 1 case and there was a normal blood pressure in the others.

A summary of the findings reported is given in Table 6. This includes all patients with renal tumors, both males and females, records of whose blood pressures were available.

TABLE 6.—SUMMARY OF FINDINGS.

| Before operation. | After operation. |
|---|---|
| **Patients with Hypernephroma: 335** | |
| 188 had normal blood pressure. | 42 still had normal blood pressure.<br>10 had hypertension. |
| | 52* |
| 144 had hypertension. | 18 had normal blood pressure.<br>28 still had hypertension. |
| | 46* |
| 3 had hypotension. | No record. |
| **Patients with other Renal Tumors: 124** | |
| 67 had normal blood pressure. | 12 had normal blood pressure.<br>4 had hypertension.<br>2 had hypotension. |
| | 18* |
| 57 had hypertension. | 11 had normal blood pressure.<br>14 still had hypertension. |
| | 25* |

* These figures represent total number of patients in the group whose blood pressure was recorded postoperatively. Records for the remainder were not available.

**Comment.** This analysis shows striking uniformity of the readings of systolic blood pressure for the various histologic types of renal tumor. Practically identical incidences for the different groups of blood pressure occurred both in cases of hypernephroma and in those of renal tumors of other types. No consistent alteration in blood pressure occurred following removal of a tumor of either type. This was particularly significant in cases of hypernephroma in which for both males and females as high an incidence of hypertension occurred after removal of the tumor as existed prior to operation. Scrutiny of the males with renal tumors other than hypernephroma would lead one to think that they experienced a diminution of arterial tension following operation, but since an exactly opposite situation existed with respect to the females, we can hardly attach significance to this. In conclusion, we found no constant increase in the blood pressure of patients who were suffering from renal tumors. In particular we failed to substantiate the observation of previous investigators: that a marked fall of an antecedent hypertension followed removal of a hypernephroma.

Finally, we would suggest that this study offers clinical evidence that an epinephrin-like pressor substance is not produced by the hypernephromatous type of renal tumor.

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## THE DOSE OF ANTIBODY EFFECTIVE IN THE TREATMENT OF PNEUMOCOCCUS TYPE II PNEUMONIA.*

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In the specific serum therapy of pneumococcus Type II pneumonia, the importance of considering the amount of serum and the time at which it is given has been recognized by a number of physicians.[1–6] The experience at the Boston City Hospital during the last 6 years has brought out the significance of these factors. It is

*This study was aided, in part, by a grant given in memory of Francis Weld Peabody by the Ella Sachs Plotz Foundation.

possible, on the basis of this experience, to offer a rational schedule of dosage for serum therapy and also to indicate some of its limitations.

The matter presented itself when we were confronted with two consecutive periods, of 3 years each, during which very divergent clinical results were obtained. During the period from November, 1929, through May, 1932, it was possible to demonstrate a considerable reduction in death rate and a rapid amelioration of fever and symptoms in cases of Type II pneumococcus pneumonia treated with specific antiserum, as compared with contemporaneous and comparable non-serum treated cases due to the same type of pneumococcus. During this period, no deaths occurred among 29 patients under 40 years of age, who were treated with serum before the end of the fourth day of the disease, and no cases were encountered in which bacteremia first developed, or extensions of the pulmonary lesions were first noted following treatment with serum.[6] In the three succeeding years, from June, 1932, through May, 1935, the effect of serum treatment on mortality was obviously less striking; clinical improvement was often delayed in the patients who recovered; and cases were encountered in which extension occurred, or in which bacteremia either developed or recurred following serum treatment.

TABLE 1.—MORTALITY AMONG CASES OF TYPE II PNEUMOCOCCUS PNEUMONIA AT THE BOSTON CITY HOSPITAL.

| | Serum treated. | | | | | | Non-serum treated. | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1929–1932. | | | 1932–1935. | | | 1929–1935. | | |
| | Number. | Died. | Per cent. | Number. | Died. | Per cent. | Number. | Died. | Per cent. |
| All cases | 48 | 11 | 23 | 38 | 16 | 42 | 148 | 76 | 51 |
| Cases with sterile blood cultures | 36 | 4 | 11 | 21 | 5 | 24 | 39 | 10 | 26 |
| Bacteremic cases | 12 | 7 | 58 | 17 | 11 | 65 | 53 | 38 | 72 |

The percentage of serum treated cases that died during the latter period was almost the same as among the non-serum treated cases (Table 1). The difference in results could not be attributed entirely to the greater incidence of bacteremic cases in the later period, since the mortality among the patients with sterile blood cultures who were treated at this time was almost the same as among non-serum treated cases. Furthermore, a number of deaths occurred among treated patients under 30 years. Nor could the differences be explained on the basis of the inclusion of cases treated with serum late in the disease or while moribund. When all patients were excluded who died within 24 hours after the first dose of serum, or who received less than 30 cc. of serum before the end of the fifth day of the disease, the differences in mortality were still great (Table 2).

Attention was then directed to the amount of serum given. The average total volume of serum per patient was only slightly less

in 1932–1935 than in the preceding period (Table 3, *A*). The total amount of antibody given each patient was then calculated, as nearly as possible, on the basis of units consistent with a Type II antibody content of 200 units assigned to Felton's standard serum F 146, or 150 units for the National Institute of Health's standard serum P 11,[7–12] and the average dose in standard units determined.* The cases treated in the years 1932–1935 now appeared to have received, on the average, only 30% of the actual amount of Type II antibody given to Type II patients during the years 1929–1932 (Table 3, *B*).

TABLE 2.—MORTALITY AMONG SERUM TREATED CASES OF TYPE II PNEUMOCOCCUS PNEUMONIA.

(Corrected by excluding: 1, patients dying within 24 hours after the first dose of serum was given and 2, patients who received a total of less than 30 cc. of serum before the end of the fifth day of illness.)

| | 1929–1932. | | | 1932–1935. | | |
|---|---|---|---|---|---|---|
| | Number. | Died. | Per cent. | Number. | Died. | Per cent. |
| All cases | 37 | 5 | 14 | 27 | 8 | 30 |
| Cases with sterile blood cultures | 29 | 2 | 7 | 15 | 2 | 13 |
| Bacteremic cases | 8 | 3 | 38 | 12 | 6 | 50 |

TABLE 3.—DOSAGE OF CONCENTRATED ANTIPNEUMOCOCCUS SERA USED IN CASES OF TYPE II PNEUMOCOCCUS PNEUMONIA.

| | *A.* Average total volume per patient (cubic centimeters). | | *B.* Average total units of Type II antibody per patient, compared with standard serum (P 11 = 150 units) (thousands). | |
|---|---|---|---|---|
| | 1929–1932. | 1932–1935. | 1929–1932. | 1932–1935. |
| All cases (as in Table 1) | 169 | 145 | 453 | 136 |
| Cases with sterile blood culture | 149 | 135 | 404 | 137 |
| Cases with bacteremia | 231 | 157 | 603 | 135 |

Although the numbers of cases were small, the increased mortality during the later years appeared to be related to the marked reduction in the actual amount of protective antibody administered. This became further evident when the cases were grouped according to the total number of units of antibody injected (Table 4). Since the number of units actually received by different patients usually depended on a prearranged program based upon volume, and since the different lots of serum used varied very widely in potency, it became necessary to interpret the effect of the dosage in the individual cases. In order to arrive at some conclusion with regard to

* The authors are deeply indebted to Dr. Felton, to Drs. Benjamin White and Elliott S. Robinson and to the Lederle Laboratories for the supply of serums. The supply of serums from Dr. Felton was made possible, in part, through the generosity of the Influenza Commission of the Metropolitan Life Insurance Company and that from the Massachusetts Department of Health was made possible, in part, through a grant from the Commonwealth Fund. We are further indebted to Dr. Felton and to Dr. L. A. Barnes for supplying the data which was essential to making the final evaluations of the serum.

the optimum dosage in these cases, it was further necessary to ascertain for each case 1, whether a poor result could be attributed to the low serum dosage and 2, whether a large dose was entirely necessary when the response to serum appeared to be favorable.

TABLE 4.—MORTALITY IN SERUM TREATED CASES OF TYPE II PNEUMOCOCCUS PNEUMONIA IN RELATION TO DOSE OF ANTIBODY AND STAGE OF DISEASE WHEN IT WAS FIRST GIVEN. (SUMMARY OF TABLE 5).

| | Dose in thousand of units of Type II antibody. | Blood culture. | Number. | Died. | Per cent. |
|---|---|---|---|---|---|
| Serum first given before end of fifth day | Less than 100 | Negative | 15 | 3 | 20 |
| | | Positive | 6 | 4 | 67 |
| | | Total | 21 | 7 | 33 |
| | 100–400 | Negative | 17 | 2 | 12 |
| | | Positive | 11 | 8 | 73 |
| | | Total | 28 | 10 | 36 |
| | More than 400 | Negative | 16 | 1 | 6 |
| | | Positive | 6 | 1 | 17 |
| | | Total | 22 | 2 | 9 |
| | All cases | Negative | 48 | 6 | 13 |
| | | Positive | 23 | 13 | 57 |
| | | Total | 71 | 19 | 27 |
| Serum first given after end of fifth day | All cases | Negative | 10 | 3 | 30 |
| | | Positive | 5 | 5 | 100 |
| | | Total | 15 | 8 | 60 |

For this purpose, the serum treated cases were all listed according to the corrected number of standard Felton units of antibody actually given and the total volume of serum, the day of the disease when its administration was begun, the mode and day of termination of the disease, and the extent of pulmonary involvement at the onset of therapy were noted (Table 5). The cases in which serum was first given after the fifth day of illness were listed separately and the bacteremic and non-bacteremic cases were segregated. From these data, interpreted with respect to the events that occurred in each case, it was hoped to arrive at a tentative conclusion with respect to: 1, a dosage, in terms of a standard unit, which could be considered adequate to bring about a good clinical response in the greatest number of cases without being unduly wasteful; 2, the sort of cases which require larger amounts and 3, an approximation of the number of units necessary in the latter cases.

It is necessary, first, to explain how the dosage was arranged in the various cases. During the earlier part of this work, conducted with Dr. W. D. Sutliff, an attempt was made to introduce a large amount of antiserum in a short interval. It was believed, empirically that immediate untoward reactions, particularly chills, could be

TABLE 5.—RELATIONSHIP OF DOSAGE OF SPECIFIC ANTIBODY TO OUTCOME IN CASES OF TYPE II PNEUMOCOCCUS PNEUMONIA.

*A.* Patients with sterile blood cultures to whom serum was first given before the end of the 5th day of illness. (a)

| Type II antibody. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Units (b) (thousands). | Volume (cc.). | First day serum given (a). | Termination of disease. Mode. | Day (a) | Age (years). | Lobes involved (c). | Case number (d) |
| 14 | 5 | 2 | Died | 9 | 52 | Ru | 70 (e) |
| 18 | 30 | 4 | Died | 5 | 34 | Rl Ll | 71 |
| 30 | 75 | 3 | Crisis | 4 | 20 | Rl | 24 |
| 30 | 30 | 2 | Crisis | 3 | 24 | Ll | 6 |
| 44 | 110 | 5 | Crisis | 6 | 35 | Rl | 21 |
| 60 | 60 | 3 | Died | 4 | 40 | Ru Ll | 73 |
| 69 | 25 | 5 | Crisis | 5 | 14 | Ru | 29 |
| 70 | 70 | 4 | Crisis | 5 | 18 | Rlm | 49 |
| 75 | 75 | 5 | Lysis | 7 | 39 | Rlm | 53 |
| 75 | 75 | 4 | Crisis | 5 | 23 | Ll | 54 |
| 85 | 85 | 3 | Lysis | 5 | 47 | Ll | 44 |
| 89 | 105 | 5 | Crisis | 6 | 15 | Rl | 58 |
| 89 | 105 | 2 | Lysis | 3 | 50 | Ru | 59 |
| 90 | 90 | 4 | Lysis | 4 | 24 | Ll | 26 |
| 100 | 100 | 4 | Crisis | 5 | 24 | Ll | 32 |
| 120 | 40 | 3 | Lysis | 3 | 24 | Rl | 7 |
| 120 | 120 | 3 | Crisis | 4 | 43 | Ll | 43 |
| 135 | 135 | 3 | Crisis | 5 | 38 | Rl | 46 |
| 150 | 195 | 3 | Crisis | 4 | 25 | Rl | 27 |
| 150 | 150 | 5 | Lysis | 7 | 31 | Ll | 51 |
| 180 | 180 | 5 | Died | 6 | 55 | Ru | 78 (f) |
| 180 | 300 | 3 | Lysis | 11 | 31 | Ll | 38 (e) |
| 190 | 205 | 5 | Crisis | 6 | 23 | Ll | 3 |
| 221 | 130 | 2 | Died | 6 | 37 | Lul | 86 (h) |
| 242 | 121 | 5 | Crisis | 6 | 39 | Rl | 8 |
| 244 | 140 | 2 | Crisis | 3 | 29 | Ll | 30 |
| 247 | 90 | 3 | Crisis | 4 | 17 | Rl | 48 |
| 264 | 220 | 4 | Crisis | 5 | 25 | Ll | 25 |
| 275 | 100 | 3 | Crisis | 4 | 14 | Rl | 31 |
| 285 | 285 | 5 | Lysis | 7 | 43 | Ru | 42 |
| 285 | 285 | 3 | Crisis | 5 | 17 | Rl | 50 |
| 315 | 105 | 4 | Crisis | 5 | 13 | Ll | 23 |
| 425 | 141 | 3 | Crisis | 4 | 31 | Rl | 12 |
| 435 | 145 | 5 | Crisis | 6 | 50 | Ll | 2 |
| 440 | 440 | 4 | Crisis | 6 | 41 | Ll | 40 |
| 470 | 150 | 1 | Lysis | 2 | 20 | Ll | 14 |
| 480 | 120 | 2 | Lysis | 4 | 40 | Rl | 22 |
| 495 | 110 | 2 | Lysis | 3 | 36 | Ll | 20 |
| 514 | 133 | 4 | Crisis | 5 | 53 | Rl | 1 |
| 550 | 200 | 3 | Lysis | 3 | 28 | Rl | 33 |
| 550 | 200 | 3 | Crisis | 4 | 29 | Rl | 35 |
| 569 | 200 | 3 | Lysis | 5 | 43 | Rl | 34 |
| 652 | 163 | 3 | Crisis | 4 | 16 | Ll | 18 |
| 730 | 162 | 2 | Crisis | 3 | 14 | Ru | 13 |
| 736 | 230 | 3 | Died | 7 | 54 | Ll | 63 (i) |
| 783 | 261 | 3 | Lysis | 5 | 24 | Rl | 16 |
| 1100 | 255 | 5 | Lysis | 7 | 53 | Rl | 17 |
| 1384 | 346 | 2 | Lysis | 6 | 24 | Ll | 15 |

(a) The day of the chill or initial chest pain is considered 1st day; except for Case 60, all cases listed under *A* and *B* were admitted within 96 hours of onset.

(b) Reduced, as nearly as possible, to a value consistent with 150 units, Type II for standard serum P 11, or F 146 = 200 units per cc.

(c) R = right; L = left; l = lower; m = middle; u = upper.

(d) Cases 1 to 37 and 60 to 71 (inclusive) were treated during 1929–1932.

(e) Bacteremia after serum. (f) Chronic and acute nephritis with uremia.

(g) Serum discontinued after 72,000 units (180 cc.), blood culture positive on 5th day; further serum given on 6th day; blood culture sterile on 7th day. Subcutaneous pneumococcus abscesses incised later.

(h) Delirium tremens; serum given through 4th day; blood culture positive on 5th day.

(i) Delirium tremens.

*B.* Bacteremic patients to whom serum was first given before the end of the 5th day.

| Type II antibody. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Units (thousands). | Volume (cc.). | First day serum given. | Termination of disease. Mode. | Day. | Age (years). | Lobes involved. | Case number. |
| 25 | 25 | 4 | Died | 5 | 28 | Ruml | 76 |
| 30 | 60 | 5 | Died | 6 | 53 | Ruml | 82 |
| 53 | 105 | 4 | Died | 38 | 35 | Ruml | 83 (j) |
| 58 | 115 | 5 | Lysis | 9 | 60 | Rul Ll | 55 |
| 70 | 140 | 4 | Died | 8 | 20 | Rlm | 80 |
| 98 | 190 | 3 | Lysis | 7 | 37 | Ll | 57 |
| 123 | 135 | 3 | Crisis | 5 | 58 | Rl | 47 (j) |
| 147 | 225 | 4 | Died | 13 | 18 | Rl | 84 (k) |
| 150 | 150 | 3 | Crisis | 4 | 44 | Ll | 39 |
| 153 | 305 | 3 | Died | 6 | 48 | Ru | 68 |
| 240 | 150 | 3 | Died | 8 | 21 | Rl Ll | 74 |
| 248 | 155 | 3 | Lysis | 4 | 27 | Rum | 41 |
| 255 | 255 | 3 | Died | 8 | 63 | Ll | 77 |
| 278 | 105 | 4 | Died | 9 | 48 | Lu | 67 |
| 295 | 230 | 2 | Died | 4 | 50 | Rl Ll | 65 (l) |
| 358 | 130 | 5 | Died | 5 | 66 | Ll | 66 (i) |
| 360 | 360 | 2 | Died | 8 | 72 | Ll | 72 (m) |
| 550 | 200 | 3 | Lysis | 8 | 36 | Rl | 36 |
| 591 | 298 | 3 | Lysis | 5 | 19 | Lu | 19 |
| 619 | 225 | 4 | Crisis | 5 | 28 | Ll | 28 |
| 795 | 265 | 4 | Lysis | ? | 37 | Rl Ll | 37 (n) |
| 1366 | 479 | 4 | Lysis | 7 | 5 | Ll Rm | 5 |
| 1935 | 430 | 5 | Died | 8 | 40 | Rl Ll | 69 (i) |

*C.* Patients to whom serum was first given after the 5th day of illness.

| Type II antibody. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Units (thousands). | Volume (cc.). | First day serum given. | Termination of disease. Mode. | Day. | Age (years). | Lobes involved. | Case number. |
| *Cases with Sterile Blood Cultures:* | | | | | | | |
| 13 | 28 | 9 | Lysis | 10 | 44 | Rl Ll | 45 |
| 60 | 120 | 6 | Lysis | 8 | 31 | Ll | 56 |
| 73 | 145 | 11 | Died | 13 | 35 | Rl | 81 |
| 75 | 75 | 6 | Died | 9 | 55 | Rl | 60 |
| 90 | 90 | 6 | Lysis | 8 | 18 | Ru | 52 |
| 183 | 61 | 6 | Lysis | 8 | 33 | Ru | 9 |
| 345 | 115 | 6 | Crisis | 7 | 13 | Ll | 4 |
| 375 | 125 | 8 | Crisis | 9 | 57 | Rl | 11 |
| 531 | 177 | 7 | Crisis | 8 | 32 | Rl | 10 |
| 675 | 225 | 7 | Died | 8 | 34 | Ru Lul | 61 |
| *Cases with Bacteremia:* | | | | | | | |
| 26 | 15 | 7 | Died | 7 | 49 | Ru Ll | 85 |
| 53 | 105 | 8 | Died | 10 | 34 | Ll | 79 |
| 105 | 35 | 6 | Died | 7 | 37 | Ruml | 64 |
| 186 | 186 | 10 | Died | 14 | 25 | Rl Ll | 75 |
| 195 | 65 | 22 | Died | 23 | 65 | Ruml | 62 |

(j) Empyema.

(k) 13,000 units 4th day; 134,000 units 5th day; blood culture sterile 6th day; bacteremia later recurred and lesion extended to Rm Ll.

(l) Delirium tremens, fractured skull, operation.

(m) Serum given (about 75,000 units daily) for 5 days; bacteremia cleared and recurred twice.

(n) Hemolytic streptococcus empyema and otitis media, erysipelas.

reduced or avoided by giving a small initial volume followed by increasing amounts up to 50 cc. Most of the cases, therefore, were given an initial dose of 5 cc., a second dose of 25, and 3 or 4 more doses of 40 to 50 cc. of the serum concentrates at intervals of 2 hours. Further doses were given after a lapse of 8 to 12 hours, the amounts and intervals usually being gauged by the condition of the patient. In the last 3 years smaller initial amounts, with a total of between 75 and 150 cc., were given, and the further treatment was not controlled in every instance. Throughout this work, changes in dosage were made for convenience or because the condition of the patient warranted it. Thus, if the first 2 or 3 injections were given late at night, an interval of 8 to 10 hours was allowed to lapse before the subsequent dose. If, in the morning, the patient was found to be afebrile or much improved, the remaining doses were reduced or omitted.

With this scheme of dosage in mind, let us consider first the bacteremic cases (Table 5, *B*) since, as judged from mortality rates, these may be assumed to be the severest cases. Of the 6 patients with bacteremia who received less than 100,000 units only 2 recovered. Since, in each of these 2 cases, an interval of 4 days elapsed between the time serum was given and the day recovery began, it is fair to assume that this recovery was probably not related to the serum therapy. Among the 11 bacteremic cases in which the total amount of antibody given was between 100,000 and 360,000 units there were 3 survivals. In each instance, clinical improvement seemed clearly related to the time of antibody administration in these 3 surviving patients. The amounts of serum were given to these patients according to a prearranged schedule of dosage based on volume, and no further serum seemed necessary. Of the remaining 6 bacteremic patients, each of whom received more than 500,000 units, only 1 died. The 5 patients who recovered were given between 465,000 and 619,000 units of Type II antibody within about 10 hours, according to schedule; the additional amounts being given because the fever and acute symptoms were not satisfactorily improved and being gauged according to the condition of the patient. In only one instance (Case 5) did the condition of the patient warrant the further use of large amounts of serum.

The deaths among the bacteremic cases, except in Cases 74, 67, 66 and 69, occurred in patients treated with serums of low potency, equivalent to 1000 or less standard units of antibody per cubic centimeter of serum (see Tables 5 and 6). In these 4 cases, other reasons militated against the full efficacy of the antibody: a hemolytic streptococcic "superinfection" in Case 74; a spread of dosage with a small total amount in Case 67, a patient with auricular fibrillation; and treatment begun on the fifth day in severely alcoholic patients with delirium tremens in Cases 66 and 69. The remaining fatal bacteremic cases may now be considered in the order that they appear in Table 5.

In the first 4 patients, less than 100,000 units were used and no effect was observed either on the bacteremia or on the clinical symptoms. In Case 84, all of the serum (174,000 units contained in 225 cc.) was given before the end of the fifth day and the blood cultures were sterile during the following 3 days. On the eighth day bacteremia recurred, and the pneumonia extended throughout the previously uninvolved lobes on the same side and also to one lobe in the opposite lung. Although the blood cultures taken 2 days later were sterile, the patient died. There was bilateral empyema at autopsy and the heart's blood culture was sterile. In Case 68, the first 135 cc. of serum given on the third day contained the equivalent of 68,000 units. The blood cultures on each of the 3 succeeding days were all sterile. Death occurred on the sixth day, after about 30,000 units had been given each day. The events in this case were practically duplicated in Case 77, except that 150 cc. of serum equivalent to 150,000 units of antibody were

TABLE 6.—RELATION OF DOSAGE OF TYPE II ANTIBODY TO BACTEREMIA AND OUTCOME IN CASES DISCUSSED IN TEXT.

| Case | | Day of disease. | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 5 | Blood culture | | | | + | +, O | O | O, C | O | | | |
| | Antibody, cc. | | | | 30 | 132 | 184 | 103 | 13 | | | |
| | Units (× 1000) | | | | 90 | 396 | 552 | 309 | 37 | | | |
| 15 | Blood culture | | O, O, O | O | O | L | | | | | | |
| | Antibody, cc. | | 100 | 80 | 81 | 85 | | | | | | |
| | Units (× 1000) | | 400 | 320 | 324 | 340 | | | | | | |
| 19 | Blood culture | | | +, + | O | O | O, L | | | | | |
| | Antibody, cc. | | | 70 | 115 | 73 | 40 | | | | | |
| | Units (× 1000) | | | 135 | 230 | 146 | 80 | | | | | |
| 36 | Blood culture | | | | +, + | O | O | O, L | | | | |
| | Antibody, cc. | | | | 110 | 90 | | | | | | |
| | Units (× 1000) | | | | 283 | 267 | | | | | | |
| 38 | Blood culture | | O | | | | + | | O | | O | Lysis |
| | Antibody, cc. | | | 120 | | | | 65 | 30 | 55 | 30 | 11th |
| | Units (× 1000) | | | 72 | | | | 39 | 18 | 33 | 18 | day. |
| 63 | Blood culture | | | O | O | | | D | | | | |
| | Antibody, cc. | | | 120 | 110 | | | | | | | |
| | Units (× 1000) | | | 384 | 352 | | | | | | | |
| 67 | Blood culture | | | + | + | O | | O | + | +, D | O | |
| | Antibody, cc. | | | | 45 | 30 | 30 | | | | | |
| | Units (× 1000) | | | | 114 | 82 | 82 | | | | | |
| 68 | Blood culture | | | + | O | O, O | O, D | | | | | |
| | Antibody, cc. | | | 135 | 65 | 65 | 40 | | | | | |
| | Units (× 1000) | | | 68 | 32 | 33 | 20 | | | | | |
| 69 | Blood culture | | | + | + | O | D | | | | | |
| | Antibody, cc. | | | 30 | 200 | 200 | | | | | | |
| | Units (× 1000) | | | 135 | 900 | 900 | | | | | | |
| 72 | Blood culture | | + | O | + | O | | + | D | | | |
| | Antibody, cc. | | 30 | 75 | 75 | 90 | 60 | 30 | | | | |
| | Units (× 1000) | | 30 | 75 | 75 | 90 | 60 | 30 | | | | |
| 74 | Blood culture | | | + | O | O | * | | D | | | |
| | Antibody, cc. | | | 150 | | | | | | | | |
| | Units (× 1000) | | | 240 | | | | | | | | |
| 77 | Blood culture | | | + | O | | | | D | | | |
| | Antibody, cc. | | | 150 | 45 | 30 | 30 | | | | | |
| | Units (× 1000) | | | 150 | 45 | 30 | 30 | | | | | |
| 80 | Blood culture | | | | + | | | + | D, + | | | |
| | Antibody, cc. | | | | 80 | 60 | | | | | | |
| | Units (× 1000) | | | | 40 | 30 | | | | | | |
| 83 | Blood culture | | | | + | | | | | | | Died |
| | Antibody, cc. | | | | 85 | 20 | | L | Empyema | | | 38th |
| | Units (× 1000) | | | | 43 | 10 | | | | | | day. |
| 86 | Blood culture | O | | | | + | D | + | | | | |
| | Antibody, cc. | | 60 | 60 | 10 | | | | | | | |
| | Units (× 1000) | | 102 | 102 | 17 | | | | | | | |

Blood culture: + = Growth of Type II pneumococci;
O = Sterile;
Cultures after death are from heart at autopsy.
Units = reduced to standard; F 146 = 200 units per cc.
C = crisis L = lysis D = died
* sputum culture = streptococcus hemolyticus; no pneumococci.

given on the first day of treatment and death occurred on the eighth day. Case 65 was in a patient admitted to the hospital with alcoholism, delirium, a fractured skull and other injuries. The pneumonia was first recognized 2 days after a bone flap had been done and was thought to have begun after the operation. In this patient, blood cultures taken before each of 9 injections of serum, given over a period of 36 hours and up to the time of death, showed an increasing bacteremia. In Case 72, 30,000 units of Type II antibody were given on the second day and from 60 to 90 thousand units injected daily during the next 5 days. Daily blood cultures were alternately sterile and positive, and death occurred on the eighth day. The course of bacteremia in relation to the dose of antibody in some of these cases is noted in Table 6.

The bacteremic patients who were treated after the fifth day of illness all died (Table 5, *C*). In 3 of these cases death occurred within a few hours after the first dose of serum was given. In the 2 patients who survived longer than 24 hours after the initial injection, the bacteremia was not affected.

Summarizing the observations in the bacteremic cases, it appeared that 1, doses of serum containing less than the equivalent of 100,000 standard units had no effect on the course of the disease at any time; 2, larger doses were ineffective when treatment was begun on or after the fifth day of illness; 3, when given before the fifth day a dose equivalent to about 150,000 units usually rendered the blood stream free of pneumococci but only temporarily; 4, while an occasional patient was completely relieved of symptoms following a total dose of less than 350,000 units, most cases required larger amounts up to 500,000 units to keep down the bacterial invasion; 5, when a total of less than the equivalent of 300,000 standard units was given, the bacteremia tended to recur and death ensued; 6, a total dose of more than 300,000 units was most effective when given in a short space of time, but when the dose was spread over more than 2 days, the bacteremia tended to recur in spite of repeated injections of serum.

The situation was different among the cases in which the blood cultures, taken before the initial injection of serum, were sterile. There were only 6 deaths among 40 patients to whom serum was first given before the end of the fifth day. Let us consider these fatal cases in the order in which they are listed in Table 5, *A*.

In Case 70, an initial injection of 14,000 units was followed by a reaction consisting mainly of dyspnea and slight cyanosis. The patient refused further injections. He later developed bacteremia and died. Case 71 was an Italian patient who could not speak English and who was moribund at the time of admission to the hospital. As far as it was possible to ascertain, his history suggested an illness of 4 days' duration. He died within a few hours after the first dose was given. At autopsy there was a thick fibrinopurulent empyema and an organizing pleuritis which indicated an illness of much longer than 4 days duration. Case 73 was a colored patient with bilateral lung involvement to whom serum was first given on what was considered to be the third day of illness. He was obviously failing rapidly at the time, but survived about 18 hours, during which time 5

doses of serum were injected. Case 78 was a patient with acute nephritis and uremia. The blood non-protein nitrogen level was 140 mgm. % on the fifth day of the pneumonia, when the first dose of serum was given. He died 24 hours later. Case 86 was a patient severely ill with involvement of the entire left lung, delirium tremens and leukopenia. Treatment with serum, on what was thought to be the second day of the pneumonia, and later with pentnucleotide failed to bring about any improvement. Bacteremia developed on the fifth day, after more than 200,000 units of antibody had been given on the preceding days. He had empyema at autopsy. Case 63 was also a chronic alcoholic patient who, in addition, had a history suggesting chronic tuberculosis. He was given a total of 736,000 units of antibody before the end of the fourth day, without apparent effect. He died 3 days later.

Among the 34 patients who recovered, the alleviation of fever and acute symptoms occurred in 22 cases within about 24 hours after the first injection of serum. In each of these cases the amount given was that decided upon beforehand and little or no further serum was given. In 10 other patients complete relief of acute symptoms was not attained until the second day after the first dose was given. Only one of these patients, Case 40, appeared sufficiently ill to warrant the use of large doses beyond the amount originally prescribed. The 2 remaining patients, Cases 38 and 15, were acutely ill for more than 3 days after serum treatment was begun.

Case 38 was a woman who miscarried a 5 months' fetus early in her disease. She received 72,000 units of Type II antibody on the third day of her illness. She was only partly improved but no further serum was given until the seventh day when a blood culture, taken on the previous day, was reported positive. She was then given doses of from 20 to 40 thousand units of antibody daily for 4 days. The bacteremia cleared rapidly but recovery was further delayed by the occurrence of subcutaneous pneumococcic abscesses. In Case 15, doses of over 300,000 units of Type II antibody were given daily for 4 days but marked improvement was not apparent until the last day of treatment (Table 6).

Among the 10 non-bacteremic patients treated after the fifth day of illness (Table 5, *C*), there were 3 deaths. This number of deaths corresponds to the death rate observed in non-serum treated cases with sterile blood cultures (Table 1). None of these fatal cases showed any obvious improvement after serum treatment. In the recovered cases, though symptoms were alleviated within 24 or 48 hours after serum therapy, it is difficult to consider a causal relationship at such a late stage of the disease. Recovery in these cases occurred on or after the seventh day of illness.

Summarizing the results noted in the non-bacteremic cases, it appeared that: 1, cases treated before the end of the fifth day usually responded with a prompt and permanent reduction of fever and alleviation of symptoms of the acute disease; 2, such a response occurred after any amount of antibody over 30,000 standard units, but in over half of the cases more than 150,000 units were actually

given; 3, the larger amounts of antibody were given, in most instances, because of the high potency of certain lots and because dosage was prescribed by volume; (4), fatalities among non-bacteremic cases occurred almost entirely in patients with other complicating conditions, including delirium tremens, or where it seemed likely that the patients were ill for a longer period than that suggested by the anamnesis—at any rate, these patients were *in extremis* when the serum was first given; 5, it is difficult to evaluate the effect of serum in the cases treated after the fifth day of illness, but no obvious benefit seemed to follow its use; and 6, in 2 of the 3 patients who developed bacteremia after serum treatment was begun, this therapy had been discontinued after less than 75,000 units had been given; in the third patient, who had delirium tremens and leukopenia, no effect was apparent from 220,000 units given over a period of 48 hours.

On the basis of the observations in these non-bacteremic cases, it seems fair to assume that recovery in almost all of the cases was related to the serum therapy when that was given before the end of the fifth day. It also seems reasonable to suppose, from a consideration of the manner in which the dosage was arranged, that the greater amounts were largely redundant. These large amounts were, in almost all instances, contained in the volume originally prescribed and these large numbers of units of antibody were due to the potency of the particular lots used. When less potent antiserums were given, the total amount of antibody, in terms of units was smaller, but it was nevertheless effective. This was also apparent when less than the full prescribed dose had been given and an interval was permitted to elapse. In many such instances no further serum was given because it was considered unnecessary.

In the light of these considerations it seems reasonable to suppose that 100,000 to 150,000 standard units of Type II antibody should prove effective in bringing about a favorable, rapid and permanent response in all but a small number of cases, provided that this amount of antibody is given before the end of the fifth day and the blood culture is sterile before the first dose is given. If this blood culture shows a growth of pneumococci, it seems necessary to give another 150 to 200 thousand units, and even more antibody may be required, persistence in treatment being essential. Optimum results seem to follow administration of the larger amounts when they are given within 24 to 36 hours after treatment is first begun. It seems unwise to permit more than 12 hours to elapse without giving more antibody to a patient in whom the fever, elevated pulse rate, or delirium persist or who otherwise looks acutely ill, unless it is ascertained that the symptoms are attributable to a process other than the Type II pneumococcus pneumonia. The patients with bacteremia who are first treated on or after the fifth day of illness apparently derive no benefit from the serum. The impres-

sion has been gained that some of these Type II bacteremic patients appear to decline more rapidly after treatment with serum, when that therapy is initiated late in the disease.

*Comment.* The goal of all therapy is primarily the saving of life and secondarily the complete and expeditious relief of symptoms. Mortality rates, particularly in a disease like pneumonia, are dependent on many factors in the host and in the invader. Large numbers of cases, therefore, must be treated and thoroughly analyzed along with comparable untreated cases before the life-saving property of a therapeutic agent can be justly evaluated. Pending the accumulation of sufficient data, the best early guide to the efficacy of a specific remedy is the rapid and complete alleviation of acute symptoms, in uncomplicated cases, after this remedy is administered. Such rapid and complete symptomatic relief has occurred in a large proportion of cases of pneumococcus Type I pneumonia when adequately treated early in the disease with Type I antipneumococcus serum. With respect to Type I cases, also, the efficacy of specific serum therapy is supported by a sufficient body of mortality figures. Much of the recent success in the use of this agent is probably attributable to those advances made in the production and concentration of Type I antipneumococcic serum which have made it possible for physicians to give large amounts of antibody with comparative ease.[8]

The report of Finland and Sutliff[6] on the treatment of pneumococcus Type II pneumonia with specific antibodies indicated that very similar symptomatic improvement could be obtained and, as far as could be judged from the small number of cases treated, the mortality could be influenced to almost the same extent as in Type I cases. During the period covered by that report, full cognizance was taken of the observations of Park and Cooper[2,3] that large amounts of antiserum are needed to establish a balance of antibody in the blood of patients with Type II pneumococcus pneumonia. In almost all cases, therefore, the serums used were selected because of their high potency in Type II antibody, and large volumes of these serums were given. During the following 3-year period, serums were used which were distributed for use in both Type I and Type II cases and had a considerably lower content of Type II antibody. During the latter period each patient received an average of only three-tenths as much antibody as was given to the cases included in the earlier report. It was felt that this drastic reduction in the actual amount of antibody given accounted, in large part, for the sharp increase in the percentage of deaths among the serum-treated cases, reaching a figure almost equal to the mortality among non-serum-treated cases. The clinical effects in the recovered cases also were not uniformly satisfactory.

The importance of having a uniform standard serum for the titration of antipneumococcus serums is evident from the data

presented. The need for such a standard has long been recognized. It was first put into use for the titration of concentrated Types I and II antipneumococcus serums by Felton[9] and recommended for international use in a specially prepared dry form by Hartley and Smith.[11,12] Such a standard is indispensable until such a time when it will be possible to titrate the biologic potency of antipneumococcus serum adequately and uniformly without the introduction of the variables in the mice and in the virulence of living pneumococci. Any discussion of dosage in terms of units of antibody becomes meaningless unless full cognizance is taken of the manner in which the antibody is titrated and unless some acceptable standard has been used for comparison.

The importance of making blood cultures before beginning serum therapy may again be emphasized. This is obvious from the data presented. Almost half of the untreated cases of Type II pneumonia in three large clinics have been found to yield positive blood cultures, and the prognostic significance of this feature is readily apparent from the differences in mortality noted in bacteremic and non-bacteremic cases in each of these series.[5,20,21] Its further importance as a guide to dosage has been noted by earlier observers[1–5] and is apparent from the data presented here. The prevention of the appearance of bacteremia has also been shown to depend on the administration of adequate amounts of antibody early in the disease.

The possibility of maintaining a balance of antibody in some cases of Type II pneumonia with unconcentrated serum of low potency was noted by Cole.[1] Finland and Sutliff[13] attempted to define the dose of Felton's serum effective in pneumonia on the basis of the cutaneous reactions with homologous type-specific polysaccharides. On reëxamining the data in the Type II cases, taking into account what has been said regarding the units of antibody, it appeared that in one instance (Case 6) the equivalent of 30,000 standard units had been given and the remaining cases had received between 100 and 160 thousand units before the positive cutaneous reactions were first elicited. With one exception (Case 5), these cases had sterile blood cultures before the antibody was given. Lord and Persons[14] failed to establish a balance of protective antibody in one Type II case with less than 200,000 Felton units, and succeeded in doing so in a second patient given more than that amount before the sixth day. Park and Cooper[3] calculated more than 500,000 units would have been necessary to accomplish this result in two of their bacteremic cases.

The use of various tests for an excess of antibody in the patient has not yet been carried out sufficiently to warrant their unqualified use as a guide to the control of dosage in Type II cases. Several such tests have been suggested including: 1, the rapid macroscopic agglutination test as used by Sutliff;[15] 2, the stained-slide microscopic agglutination test of Sabin;[16] and 3, the skin test with the

homologous type-specific polysaccharide (Tillett and Francis[17]), as adapted to the control of dosage in Type I cases by Francis.[18] The latter test is probably the most desirable since it is a tissue reaction. Occasional patients, however, fail to give the characteristic response regardless of complete recovery with an excess of antibody, and others fail to recover after a positive test has been elicited.[13] It is felt that the blood culture, the presence of fever, elevated pulse rate and evidences of "toxemia" and the response to earlier doses, if sufficiently large, probably serve as the most useful and practical guides for continuation of antibody therapy in the individual case.

Based upon the observations in the present cases, a tentative plan of dosage based upon a standard unit is proposed which may be expected to give the optimum effect on the mortality rate in any group of cases and on the clinical condition of the individual cases. This dosage may seem somewhat wasteful but appears to be warranted by the data at hand, and takes into account the danger of giving smaller amounts to the severer cases, in which valuable time may be lost. It must be kept in mind, however, that these recommendations are based on a comparatively small number of cases and may require modification as more data become available.

The experiences of the past few years with Type I cases, both in this country and in Great Britain, have shown quite clearly the advantage of having potent concentrated antiserum which enables physicians to give large amounts of specific antibody in a small volume and with a comparatively small amount of total solid. It is desirable, therefore, to do the same for Type II cases. Since concentrated serums of high potency in Type II antibody are comparatively difficult to make with great regularity, it would seem helpful to withhold from distribution for use in Type II cases serums of low potency in antibodies for this type. About 1500 standard units per cubic centimeter would be a reasonable minimum, and higher concentrations than this are preferable if they can be attained without excessive amounts of total solid. With such serums, physicians would be more inclined to treat their patients adequately.

The occurrence of the so-called "zone phenomenon" in the interaction of pneumococcus antigens and antibodies raises the question of a possible harmful effect of excessive dosage. Such zone phenomena have been demonstrated for agglutination, precipitins, phagocytosis and passive protection of mice, but have not been observed in the results of treatment in human cases (see Ward[19]). The test-tube experiments do not take into account the large reservoir of neutralizing material which is present in the infected lung.

The results of therapy have been considered here primarily from the point of view of dosage. Other features of serum therapy have been considered elsewhere.[6] A more detailed analysis of all the Type II cases is included in a separate communication.[21]

**Conclusions.** Clinical attempts to determine the proper dose of serum in the treatment of cases of pneumococcus Type II pneumonia have emphasized the importance of having a uniform standard with which the potency of various lots of Type II antipneumococcus serums can be compared. The adoption of an international standard, as proposed by Hartley and Smith, is highly recommended.

A tentative plan of dosage for Type II cases is offered, which is based upon observations on the effect of various amounts of antibody:

1. When a diagnosis of Type II pneumococcus pneumonia is made, an amount of Type II antibody equivalent to 100,000 or, preferably, 150,000 units of the proposed standard serum should be given to the patient in as short an interval as is consistent with the avoidance of untoward reactions.

2. An additional 200,000 units should be given to all cases showing Type II pneumococci in the blood culture. This amount should also be given in as short an interval as is consistent with safety and even in spite of apparent improvement in the patient's condition.

3. Additional amounts of 50,000 to 100,000 units should be given at intervals of 6 to 12 hours in all cases until the fever and other acute symptoms are relieved, or until it is shown that these symptoms are not due to the Type II pneumococcus pneumonia.

4. After treatment is once begun, it is unwise to permit an interval of more than 12 hours to elapse without giving further serum, unless the patient is relieved of fever and serious symptoms.

Treatment with antibody beginning after the end of the fourth day of illness is probably of no benefit, except possibly in non-bacteremic cases, and then only if it is begun during the fifth day.

The results of blood cultures are the most important guide to serum dosage in addition to being of great prognostic significance.

The interests of physician and patient are served best if only serums of high potency in Type II antibody are released for treatment of patients with pneumonia due to this type.

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## EPIDEMIC PLEURODYNIA.

### ("DEVIL'S GRIP") IN CINCINNATI.

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ELEVEN cases of epidemic pleurodynia occurring among the personnel of this hospital are described in this report. The first case was seen on June 18 and the last on September 25, 1935. They are typical of cases reported in the literature as well as of numerous other cases seen by physicians in Cincinnati during the same period.[1]

Outbreaks have been reported from the Eastern and Southern States of this country since the disease was first noted here in 1888.[2,3,4] Daae and Homann, of Norway, are given credit for the early, if not the first, description of the disease in medical literature.

As described in the literature, the disease is said to occur in paroxysms lasting 24 or more hours. These are characterized by

sudden onset of excruciating pain in the chest or epigastrium, the pain being aggravated by deep breathing or movement of the trunk; often a chill; fever of 100° to 105° F.; tenderness, frequently persistent, and usually over the site of pain; a normal white cell count or leukopenia; and the absence of important pleural or pulmonary physical findings. It occurs during the summer months, attacking healthy young people of either sex, more commonly children, and frequently several members of the same family. It may subside after one paroxysm, or there may be one or more recurrences after a period of 24 to 30 hours of comparative comfort. Recovery is usually prompt and complete, although Churchill[5] reports that the recovery in his patients was slower than the severity of the acute symptoms would seem to warrant.

The etiology of the disease is not known. Small[6] described a protozoan organism within the erythrocytes of 2 patients with the disease. Failure of other workers to confirm his findings should not cause a careful blood study to be omitted.

The nature and location of the pathologic lesions are unknown. It has been suggested that they might be a myositis of the chest wall and back.[4] However, no microscopic studies of the apparently affected muscles have been reported.

The outbreak described in this paper is apparently the first one in the Middle West. A microscopic study of the muscles was made in 1 patient. Since the patients comprising the reported group were interns and nurses, an excellent opportunity for observation was had. For these reasons this communication is made.

**Description of Cases.** Of the 11 cases diagnosed as epidemic pleurodynia, 8 were admitted to the hospital and 3 were treated as office patients. This description will be confined to the former, although the latter were similar, but could not be observed so closely.

Of those admitted to the hospital, 5 were nurses, 2 interns and 1 the wife of a physician. There were 7 women and 1 man, their ages ranging from 18 to 25 (average 21). All had been in good health until the onset of their present illness.

*Prodromal Symptoms.* Four of the patients gave a history of feeling tired and "dragged out" for 2 to 7 days prior to the onset of acute symptoms; 2 had vague, generalized abdominal cramps not associated with nausea, vomiting, or diarrhea.

*Onset.* In half of the group the onset was abrupt with excruciating pain in the epigastrium and along the anterior costal margins, the pain being aggravated by movement or deep breathing; in the remainder the pain was minimal at first but gradually grew worse, reaching a maximum of intensity in 4 to 12 hours after its first appearance.

*Symptoms.* Pain: This was the most prominent feature of the disease. Inspiratory chest pain, described as being cramp-like in character, was the most common type, although in 1 patient the

pain associated with the first paroxysm was epigastric, being increased more by movement of the trunk than by deep inspiration. In 4 the pain was localized to the left chest and hypochondrium with each paroxysm. In the others the pain alternated with each side of the chest in the succeeding attacks. In 1 instance, right lower quadrant abdominal pain preceded the appearance of pain in the right chest by 4 hours. Three of the group were entirely free of pain between paroxysms; the others had slight pain on deep inspiration. Tenderness over the site of pain, although hard for the patient to localize, was a constant finding even between paroxysms. It did not persist for longer than 1 day after the termination of the acute symptoms.

Fever: The fever usually followed the pain, there being a lag of a few hours between the onset of the pain and the fever, while the reverse was true at the end of the paroxysm. The "pain-fever" relationship, however, was very close. It was the predominant symptom in each recurrence except one in which the patient's third paroxysm of pain was not accompanied by fever. The elevations in temperature ranged from 99.4° to 104° F. The pulse rate increased in proportion to the fever.

*General Symptoms.* Aside from the epigastric and right lower quadrant abdominal pain and the prodromes already mentioned, symptoms referable to the abdomen and gastro-intestinal tract were not noted. All of the patients except 1 felt well during the interval between attacks. Headache, generalized muscular aching, weakness, and loss of appetite were not prominent symptoms. None of the patients complained of cough, and none gave a history of recent acute respiratory disease.

*Number of Attacks or Paroxysms.* Five of the patients had 3 paroxysms; 1, 9; 1, 2; and 1, 1. Most of the attacks were sharply defined, so much so that in many cases the time of onset of the succeeding ones could be fairly accurately predicted. The third attack was always the most severe.

*Physical Findings.* During the height of an attack the skin was flushed, moist and hot, but no skin eruptions, aside from herpes labialis, were observed. Tenderness over the site of the pain was a constant finding and protective splinting of the affected chest was common. Persistent, fine râles at the base of the axilla were noted in 1 patient. Aside from this instance, no pulmonary or pleural signs were detected. One patient, whose illness was similar in all respects to the others reported here, and on whom a biopsy of a muscle of the chest wall was taken, developed a pleural friction rub 5 days after his discharge from the hospital. A hematoma which had developed in the wound may have played a part in the production of this physical sign. However, his case is not included in this series.

*Laboratory Findings.* The leukocyte count averaged 7400. White cell counts taken after the fifth day of the illness on 3 patients averaged 5000, while counts on the other 5, taken within the first two days of the illness, averaged 9900. The neutrophils varied from 54 to 78% and in no case was eosinophilia noted or were intracellular sporozoa found. The urine was negative. Blood cultures taken in 6 cases were sterile.

*Muscle Biopsy.* A section of the apparently affected latissimus dorsi muscle was taken from one of its slips of origin on the lower chest wall. Cultures of the tissue were sterile. Microscopic study revealed no morphologic change.

*Roentgen Ray Examinations.* All patients had had a Roentgen ray examination of the chest within 6 months of the time of their admission to the hospital. Five, as part of a yearly physical examination, had had the examination 3 weeks prior to their illness. Further examinations were made during the illness and were repeated on an average of 6 weeks after discharge. No change in the findings was noted during these periods.

*Duration.* The average duration of the illness as judged from the first attack of acute pain and fever until the termination of the last paroxysm was 5 days.

*Convalescence.* Six of the patients experienced occasional fleeting chest pains for 4 days after discharge, stating that they felt well after these had disappeared. One patient had chest pain, lasting from a few minutes to as long as 1 hour, for a month. She did not feel badly otherwise. Another experienced similar pain for 2 months and felt tired for 3 weeks following her discharge. When last seen, late in September, 1935, all of the patients were free from symptoms and in good health.

**A Typical Case.** Dr. Nina A., a woman intern, aged 24, developed pain of an inspiratory nature in the left side of the chest at noon, July 19, 1935. She was seen 2 hours later, at which time the temperature was 99° F. Examination of the chest was negative aside from tenderness over the lower left anterior costal margin. Six hours after the onset the temperature was 102° F., the pulse was 110 and the respirations 25. The pain was very severe, being aggravated by movement or inspiration. Her past history was not remarkable. She had been in good health until the present illness. Routine Roentgen ray examination of the chest 2 weeks previously had been negative. The first paroxysm of pain and fever lasted for 36 hours. Following this was a 24-hour interval of comfort. At the end of this period a second paroxysm lasting 24 hours occurred. This was followed by a comfort interval of 30 hours, then a third paroxysm lasting 24 hours (Chart I). The pain was the most severe in the last recurrence. At the end of the third attack she felt quite well and remained so until discharge, 5 days later. Repeated examinations of the chest were negative. A Roentgen ray film of the chest on the day of admission showed no change from the one taken 2 weeks previously. The urine was negative. A blood culture taken, July 25, was sterile. The leukocyte count on the second day of the illness was 8600. The blood smear showed 70% neutrophils, 28% lymphocytes and 2% monocytes. On July 27, a small section of the latissimus dorsi muscle was removed from one of its slips of origin in the left

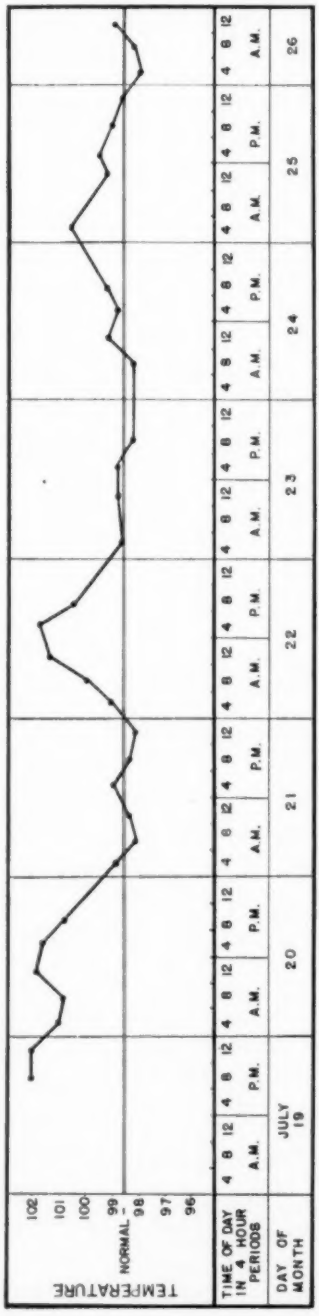
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CHART I.—Temperature in the case reported.

chest wall. Cultures of the muscle were sterile. Microscopic studies did not show any morphologic changes.

The patient was discharged from the hospital after 12 days, and when last seen, September 20, 1935, she was in good health. A Roentgen ray film of the chest at this time showed no change from those taken previously.

**Summary.** Eleven cases diagnosed as epidemic pleurodynia are reported. They were apparently a part of an epidemic occurring in this area.

In this small series of cases, the majority had 3 recurrences, the third one being the most severe. One-half of the patients had prodromal symptoms and a gradual onset. The pain preceded the fever, but the "pain-fever" relationship was close. Tenderness over the site of pain did not persist after the acute symptoms had subsided. The pain was described as cramp-like in character. There were no important pleural or pulmonary findings either on clinical or repeated Roentgen ray examinations. Leukocyte counts in 5 cases taken during the first 2 days of the illness were normal. Those taken after the fifth day (3 cases) were low.

This is the first reported outbreak of the disease in the Middle West.

Microscopic study of the apparently affected muscle of 1 patient did not show any morphologic changes. This is the first such study to be reported and should be repeated on a large number of patients.

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## EPIDEMIC MYALGIA OR PLEURODYNIA IN SOUTHWESTERN OHIO.

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In this portion of the United States, epidemic pleurodynia was first diagnosed in the summer of 1935. The initial recognition came from at least four independent sources; two hospital physicians, a general practitioner and a district physician of the Cincinnati Health Department. Through newspaper accounts of "devil's grip,"

the clinical picture was subsequently so well publicized that laymen often diagnosed the typical cases before summoning a physician, or did not summon one at all.

It has been stated[1] that epidemics of this condition were first recorded in Iceland (1856) and Norway (1872), and also in England, Denmark, Sweden, Finland, Germany and Portugal. Local names are frequently given to the disease, such as "Bornholm's Disease" after the Island of Bornholm, and "the Bamle disease" in Norway. In England the term "epidemic pleurisy" is popular. "Epidemic myalgia," the name preferred by some,[1] is based on the assumption that the pain has its origin in the muscles of the chest and abdomen; "epidemic pleurodynia" is the name which seems to have the most general use in the United States at the present time. The American reports of epidemic pleurodynia are summarized in Table 1. When the disease was first recognized in Cincinnati during the summer of 1935, the Health Department requested that physicians report it on the regular communicable disease forms. The total of 282 cases is probably much less than the actual incidence of the disease because so many were not seen by physicians. Chart I gives the onset of reported cases during the weeks of the epidemic. Communications with several private hospitals and practising physicians show that the disease also appeared in the nearby portions of Ohio and northern Kentucky.

TABLE 1.—PREVIOUS AMERICAN EPIDEMICS.

| Author. | Title of article. | Location. | Year of epidemic. | Season. | No. of cases. |
|---|---|---|---|---|---|
| Dabney[2] | Account of an epidemic resembling dengue which occurred in and around Charlottesville and the University of Virginia, in June, 1888 | Virginia | 1888 | Late spring and early summer | 29 and "at least as many more." |
| Reilly[3] | An epidemic of intercostal neuritis | New York City | 1899 | Late spring and early summer | 14 |
| Reilly[4] | An unusual pain syndrome associated with the present wave of influenza | New York City | 1921 | Late spring and early summer | "Group. |
| Payne and Armstrong[5] | Epidemic transient diaphragmatic spasm | Virginia | 1923 | Summer | 27 |
| Hanger McCoy and Frantz[6] | An epidemic of mild fever of unknown nature | New York City | 1923 | Summer | 16 |
| Greene[7] | Epidemic pleurodynia? | New York City | 1923 | Summer | 141 |
| Torrey[8] | Epidemic diaphragmatic pleurodynia or "Devil's Grip" | Philadelphia, Pa. | 1924 | Summer | 4 |
| Churchill, Landis and Glusker[9] | An epidemic of undetermined nature: dengue? | Cape Cod, Mass. | 1926 | Summer | 50 |
| Richter and Levine[10] | Epidemic pleurodynia | Boston, Mass. | 1933 | Summer and early fall | 24 |
| Crone and Chapman[11] | Epidemic pleurodynia | Boston, Mass. | 1933 | Summer and early fall | 30 |
| Callaway[12] | Epidemic pleurodynia | Durham, N.C. | 1934 | .... | 29 |

This study is based only on the 282 cases reported from Cincinnati. Although the material is primarily epidemiological in nature,

some of the reporting physicians sent in clinical and laboratory data which are of interest.

**Epidemiologic Aspects.** The summer weather of Cincinnati tends to be warm and moist. There was a little more rain in the summer of 1935 than normal, and the average temperature was a little elevated above normal, but the deviations were not striking.

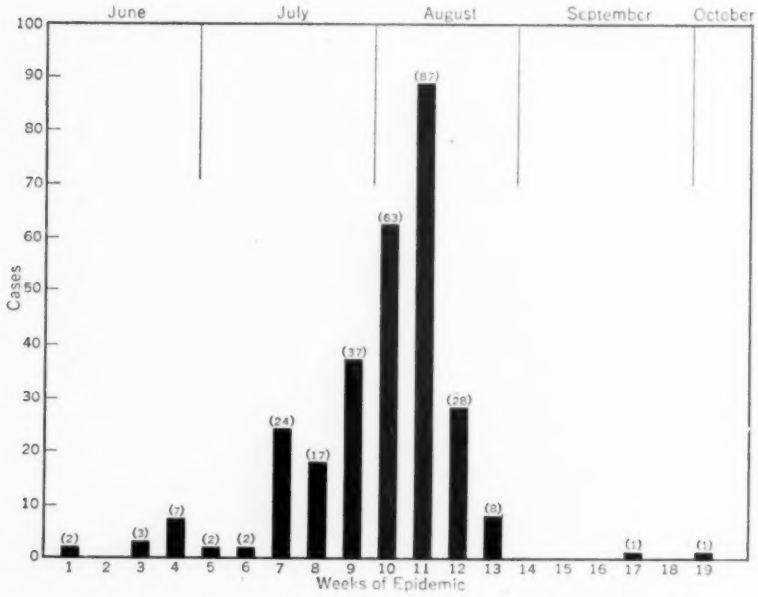


CHART I.—Occurrence of epidemic pleurodynia in Cincinnati by weeks.

Distribution between the sexes is approximately equal; of the 282 cases, 145 (51.4%) occurred in males, and 137 (48.6%) in females. (In the population as a whole there is a slight preponderance of females.)

The colored and white races appear to be about equally susceptible; 36 cases (12.8%) occurred in the colored inhabitants who make up 11.3% of the total population.

Although no age group is exempt, the tendency to affect predominantly children and young adults has been commented on by several writers on the subject, and is borne out by the observations in this epidemic. Table 2 shows the actual incidence by age groups; while Chart II shows the incidence rate per 100,000 in the same groups. Calculations are based on the 1930 census figures.

The cases were well distributed over the city, showing no predilection for the rich or poor, sanitary or insanitary, screened or unscreened houses. The "basin" is the older portion of Cincin-

nati, and is comprised of Census Tracts 1 to 11, 14 to 17, and 91. It lies along and near the Ohio River bank, and is the area where poverty and congestion are most prevalent and the screening of houses is at a minimum. This area contains 28% of the city's population and accounted for 29.4% of the cases of epidemic pleurodynia reported.

TABLE 2.—REPORTED CASES BY AGE GROUPS.

| Age. | Cases. | Age. | Cases. |
|---|---|---|---|
| Under 5 yrs. | 73 | 35 to 44 yrs. | 18 |
| 5 to 9 yrs. | 55 | 45 to 54 yrs. | 5 |
| 10 to 14 yrs. | 33 | 55 to 64 yrs. | 3 |
| 15 to 19 yrs. | 31 | 65 to 74 yrs. | 0 |
| 20 to 24 yrs. | 17 | 75 yrs. and over | 2 |
| 25 to 29 yrs. | 29 | | |
| 30 to 34 yrs. | 16 | | 282 |

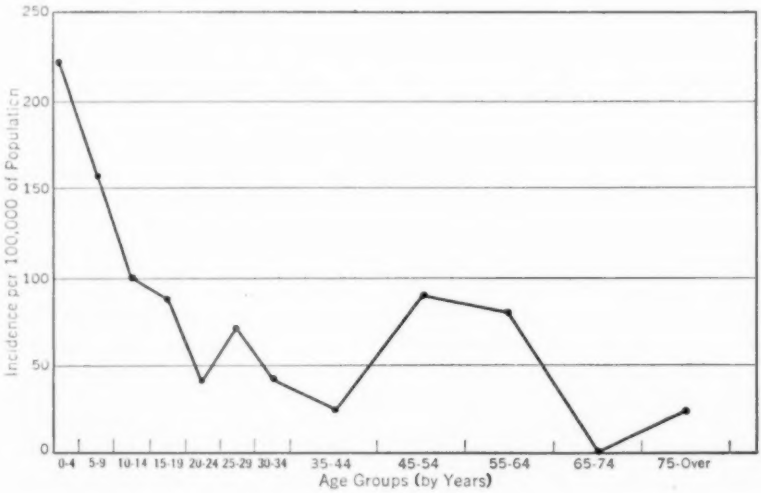


CHART II.—Incidence by age groups.

European authors[1] clearly recognized the communicability of the disease, although this fact has not been so promptly recognized in the United States, perhaps because of the negative view expressed by Dabney[2] in 1888. In this country the best demonstration of the communicability of the disease was made by Greene[7] who reported an epidemic occurring in a children's home in New York City; 11% of 1230 boys were affected, while the girls' department on the other side of the street had not a single case. The reason was that there was no intermingling of the boys and girls, although the climatic and mosquito surroundings were the same, as were also food, milk and water supplies.

In the Cincinnati epidemic 24 groups of contact cases were

noted. Of the 244 localities from which cases were reported 24 (9.8%) had more than 1 case. Not enough data are present for an exact expression of the communicability index.

No exact observations of the incubation time were made, but contemplation of the epidemic as a whole, and of groups of cases confirms the generally accepted view that the incubation period is short, in the neighborhood of a week.

**Clinical Aspects.** The diagnosis of epidemic pleurodynia is made almost entirely on a clinical basis, and with practically no help from the laboratory. Because of the unusual interest which the disease aroused in Cincinnati the attending physicians appended a few clinical notes to their reports in 86 instances. Such data are valuable from the positive side because they tend to present features which impressed the attending physicians, but have no significance from the negative side.

Of 77 cases in which single temperature readings were given, 45 (58.4%) lay between 101° F. and 103° F. The upper extreme was 104.6° F., and 4 normal readings were reported. The pulse rate was elevated approximately in proportion to the temperature, and in no case was it reported as slower than normal. Chills were mentioned 7 times, chilly feelings once, general malaise twice, headache 23 times. Recovery was usually complete in 4 to 5 days, often less, and seldom longer. The characteristic feature of the disease is the sudden onset of severe pain in the general region of the line of diaphragmatic attachment to the thoracic wall. It is intensified during respiration. Usually it is unilateral and predominantly on the thoracic side of the diaphragm, but not infrequently the abdominal features are striking enough to effect the simulation of an acute condition requiring surgical intervention. The pain tends to come in paroxysms, and may shift from one side of the thorax to the other. Frequently, there is tenderness of the chest wall along the line of diaphragmatic attachment. At the end of 12 hours considerable improvement is usually shown. This may signify the termination of the disease, but generally a relapse occurs on the third or fourth day almost as severe as the onset. From then on recovery is usually speedy. No complications, no fatalities, and no prolonged convalescences were observed. One case was reported in which a second attack occurred 20 days after the initial onset; whether this is to be regarded as a relapse or reinfection is a difficult distinction to make.

Physical signs are not very striking. Rapid shallow respiration because of pain is characteristic. The skin is hot because of fever. Friction rubs are infrequent; only two were mentioned in reports. This agrees with the experience of American authors who have recorded none, or a low incidence; it differs somewhat from the experience of the English authors, Williamson,[13] Lloyd[14] and Atlee, Amsler and Beaumont[15] who found friction rubs in over half

of their cases. Possibly the fact that most of the Cincinnati cases were studied in the home prevented the detection of transient friction rubs which might have been disclosed during more close observation in a hospital. One of the two friction rubs reported lasted only for a short time. The other persisted for a week after subsidence of the acute symptoms. This occasionally prolonged persistence of the rub has been commented on by Williamson.[13]

In only 9 cases were blood counts reported. Most of them were within normal limits. Two leukocyte counts were above 10,000. One of them subsequently fell to 3000, the only leukopenia in the group. Such a cycle, if common, would explain the contradictory reports in which some authors have described a leukocytosis and others a leukopenia. No plasmodia were found in any blood smears.

*Differential Diagnosis.* A few cases are suggestive of coronary thrombosis because of pain referred to the substernal region. Early pneumonia, pericarditis, and diaphragmatic pleurisy must also be considered. The chief danger arises when there is enough abdominal pain to suggest a surgical condition. Knowledge of the disease is the best safeguard against unnecessary operation. Usually the picture is characteristic enough to make the distinction easy, but at times it is very difficult. One very capable local surgeon informed us that he had removed three normal appendices in patients whose subsequent course showed them to have been afflicted with epidemic pleurodynia. At the time of the third operation he knew of the epidemic, but the picture of appendicitis was so closely simulated that he performed the operation. He observed that the appendix was normal, but the entire peritoneum had a somewhat violaceous tint.

*Therapy.* Therapy consists in relief of the severe pain and assurance that recovery will be early and complete. Occasionally, large doses of morphin do not completely control the pain.

*Etiology and Mode of Transmission.* The cause of the disease remains unknown. Attempts made in this epidemic failed to confirm the plasmodium theory of Small.[16] From observation of cases the spread seems to be through direct contact.

*Pathologic Anatomy.* There were no postmortem studies in this benign disease. Doctor Welborn's[17] study of a biopsied intercostal muscle was negative.

*Immunity.* In an epidemic involving only one season nothing can be said concerning permanent immunity.

**Case Reports in one family.** This family group illustrates the characteristic symptoms of typical and mild cases and suggests an abortive case. The relative immunity of adults in indicated, also the communicability of the disease. This white family is a rather healthy one, perhaps slightly below the comfort level financially, but well above the subsistence level.

CASE 1.—Harry H., aged 8 (typical case), was admitted to the Cincinnati Children's Hospital July 16, 1935. On July 14, 1935, he complained of pain in his stomach and had a temperature of 103° F. On the second day

he was symptom free and temperature was normal. At 4.00 P.M. on the third day he complained of pain in the left side of his chest and in his abdomen. His temperature rose to 103° F. General malaise, headache, and some nausea were present, but no vomiting. Physical examination showed grunting respiration, muscle spasm all over the abdomen, and tenderness localized to the epigastrium. Recovery was uneventful after the third day of illness.

CASE 2.—Ruth H., aged 6 (typical case), had her onset and was admitted to the same hospital on July 19, 1935. The hospital record reads: "This 6-year-old white female took sick this A.M.—pain in right flank. This was most complained of on inspiration. Child has not vomited, but fever has been complained of since onset of pains. Temperature 102° F. at present." General physical examination was negative except for fever; on July 20, 1935, temperature was normal; on the evening of July 21, 1935, temperature was up to 102.4° F. Recovery thereafter was rapid.

CASE 3.—John H., aged 10 (mild case), on the afternoon of July 20, 1935, on arrival at a picture theater, was suddenly stricken with such severe pain low in the left side of the chest and in the epigastrium that he fell to the sidewalk. Companions helped him home, and his symptoms cleared up in about 24 hours. No physician was consulted during this illness.

CASE 4.—Carl H., Jr., aged 14 (mild case), on the evening of July 27, 1935, went to the office of a district physician of the Cincinnati Health Department because of a slight discomfort low in the right side of his chest. The district physician said—"Carl if you were sicker I should say that you had the 'Devil's Grip' that the newspapers are so full of now." Carl H., Jr., then gave the information that other members of his family had been stricken with typical severe manifestations of the disease. His temperature and physical findings were normal. The symptoms were not severe at any time, and his recovery was rapid.

CASE 5.—Stephen H., aged 4 (possible abortive case), on July 29, 1935, had a temperature of 102° F., poor appetite and some malaise but no pain. By the next day he had recovered completely.

The parents, Carl H., Sr., aged 47 and Catherine H., aged 36, remained well during the epidemic, as did 2 other children, William, aged 6, and Barbara, aged 14, who were away from home.

**Conclusions and Summary.** 1. Epidemic myalgia or pleurodynia is an acute communicable disease characterized by severe pain in the region of the diaphragmatic attachment to the thoracic wall.

2. During the summer of 1935 an epidemic of this disease occurred in Cincinnati, Ohio, and 282 cases were reported to the Health Department.

3. Children are more susceptible than adults.

4. White and colored, male and female, sanitary and unsanitary individuals are about equally susceptible.

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## ROCKY MOUNTAIN SPOTTED FEVER IN PENNSYLVANIA.

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According to the United States Public Health Service records,[1] only 3 cases of Rocky Mountain spotted fever have been reported to it from Pennsylvania, in 1930, 1932 and 1934, from Franklin, Delaware and Chester Counties, respectively. A case observed at the University Hospital, during June, 1935, is presented here in order to emphasize the salient features of the disease, and to remind the physician that the condition is no longer a medical curiosity in this region of the United States. We believe that the incidence of the disease, perhaps in a milder form, is greater in this section than these reports would indicate, due possibly to the failure voluntarily to report the disease, or to faulty diagnosis.

The disease was recognized in the Bitter Root Valley in Montana as early as 1873, but the clinical picture was first described by Maxcy,[2] in 1899. Since its recognition, Rocky Mountain spotted fever is known to have recurred from year to year, with little variation in locality throughout states of the Rocky Mountain region. Rumreich *et al.*,[3] in 1931, reported the first recognized cases in the East, from Delaware, Maryland, Pennsylvania, Virginia, North Carolina, and the District of Columbia. Since this report a number of other workers[4] have noted the appearance of the disease in this section of the country. How long it has existed in this section, and how extensive has been its spread elsewhere, is uncertain. It is known, however, that the disease is widespread

among many wild rodents, and is transmitted to man by the bite of an infected tick. The virus was demonstrated in these vectors by Ricketts.[5] The Dermacentor variabilis ("wood tick" or "dog tick"), shown to be the predominant carrier in the East,[3] appears in March, becomes most prevalent from May to July, and is occasionally found as late as October. Since these infected ticks usually remain undetected until man contracts the disease, the epidemiological character and geographic distribution of the disorder is based primarily upon human case reports. At present, the data indicate a focal endemic distribution, but sufficient information is not yet available for accurate delineation of the infected localities.

Rocky Mountain spotted fever may be briefly defined as an acute, endemic, infectious but non-contagious disease, widespread among many wild rodents, and transmitted to man by infected ticks. It is characterized clinically by onset with chills; a continued fever terminating usually by rapid lysis after 2 or 3 weeks; headache, muscle and joint pains; a macular eruption which becomes petechial, appearing about the fifth day on the wrists, ankles and back, and then spreading over the entire surface of the body. Convalescence[6] may be protracted but is usually complete; the fever is occasionally followed by deafness, visual disturbances, slurring of speech and mental confusion for a few weeks. The mortality in the eastern United States is about 25%.[7] The pathologic findings[8] are referable to the vascular system, where endothelial proliferation is followed by thrombosis, occlusion and perivascular accumulation of large mononuclear cells, particularly in the skin, brain, spleen and lymph nodes.

Although the clinical course and the character of the exanthem leads one to suspect the disease, the diagnosis must be confirmed by laboratory studies. At some stage of the disease, usually by the end of the second week, the blood contains sufficient specific agglutinins for one or more strains of proteus X, as demonstrated by the Weil-Felix reaction. Davis[9] emphasizes the importance of a second test about the twentieth day, if the first specimen taken between the tenth and fifteenth days fails to show these agglutinins. It is desirable to test the serum against proteus X–2 as well as X–19, as the former may be positive even when the latter is negative.

The Weil-Felix reaction is also positive in typhus fever. Rocky Mountain spotted fever, a tick-borne infection, occurs usually in the late spring and summer months. The rash is first noted on the wrists and ankles, with rapid extension over the trunk, face and extremities, including the soles and palms. Typhus fever, on the other hand, a flea- and louse-borne infection, is most commonly seen in the fall and winter months. The rash makes its first appearance on the body, and unless the case is quite severe will not spread to the face and extremities. If necessary, guinea-pig inoculation

and cross-agglutination tests are available through the Public Health Service to establish the diagnosis.

Since the disease is self-limited, and specific therapy unknown, symptomatic treatment and supportive measures must be relied upon.

**Case Report.** A. T., a white woman, aged 43, was admitted to the private service of Dr. Alfred Stengel, on June 16, 1935. Except for a chronic arthritis of 10 years' duration, she was well until June 9, at which

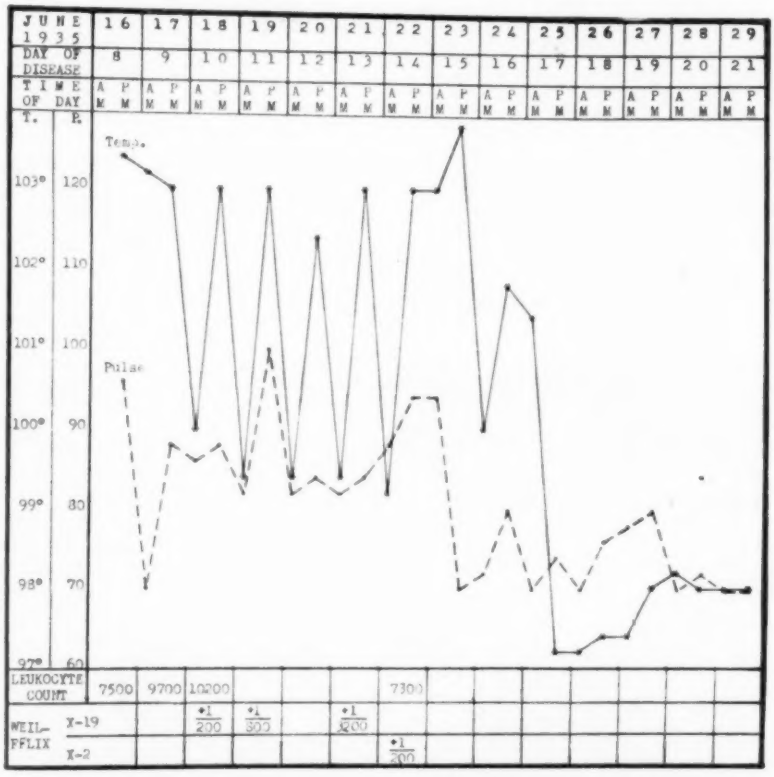


CHART I.—Showing the temperature, pulse rate, leukocyte count and agglutination reactions during hospitalization.

time a feeling of general malaise and lassitude forced her to bed. The following morning she complained of pain in her back and stiffness of all her joints. That night she experienced a severe chill, followed by a sudden rise in temperature (103° F.), generalized headache, and multiple joint pains. On June 12, there appeared rose-red spots on her knees and ankles, and next day the buttocks, wrists, abdomen and back were likewise involved. The elevation in temperature (101° to 103° F.), the multiple joint pains, the progressive skin lesions, and the severe headache persisted until her admission to the hospital. The patient had not been out of the immediate vicinity of her suburban home in Delaware County for several

months. There was no evidence of rodent infestation and her home sanitation was above reproach. About 2 weeks prior to the onset of her illness, the patient removed several ticks from her dog, but denied having been bitten.

FIG. 1.—Photographs taken on the fourteenth day, showing the general distribution and petechial character of the eruption at this stage.

On physical examination, one found an acutely ill white woman, with temperature 103.2° F., pulse 96 and respirations 20. The entire skin

surface, excepting the face, was covered by a macular eruption, varying in color from red to almost purple, and measuring from 2 to 5 mm. in diameter. Some of the spots disappeared on pressure. All of the joints were painful, and there was generalized muscular tenderness. The tongue was heavily coated. Examination of the heart and lungs was negative except for the presence of a rather harsh systolic murmur heard over the apex of the heart. Laboratory studies showed 4,300,000 erythrocytes, 83% hemoglobin (Sahli), 7500 leukocytes, a normal differential picture and essentially normal urine.

After admission (Chart I) the patient continued to have an elevation of temperature, as well as joint and muscular pains. The chief complaint, however, was severe headache, intensified by ocular movement, and described as being worse than those suffered during an attack of typhoid fever (1910). At the height of the illness, she experienced terrifying dreams, chiefly during the daytime. The rash (Fig. 1) soon spread over the face and oropharynx. The first Weil-Felix reaction (X–19) on the tenth day was positive in a dilution of 1 to 200, and 3 days later in a dilution of 1 to 3200. On the fourteenth day, using X–2 strain, it was positive in a dilution of 1 to 200. The spleen was first palpable about the sixteenth day of the disease. On the seventeenth day the pyrexia subsided almost by crisis, and the rash began to fade. The patient was discharged on June 30, after an uneventful complete recovery.

**Summary.** 1. The case of a patient with Rocky Mountain spotted fever acquired in Delaware County, Pennsylvania, is presented.

2. Physicians should be aware of the presence of this disease in the eastern United States, especially in rural sections, during the spring and summer months.

3. The importance of reporting all cases as an aid in the epidemiologic study of the disease is stressed.

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# ENCEPHALOMYELITIS FOLLOWING GERMAN MEASLES.

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It has been the general impression that German measles is a benign disease and that symptoms indicating involvement of the nervous system do not occur. Considering the frequency of the disease this impression is understandable. However, there is an increasing number of cases being recorded in the literature with very severe neurologic symptoms. We have seen 4 such cases in the past few months in Massachusetts, where there has been an epidemic of German measles. It is the purpose of this article to report the findings in 4 cases of German measles in which the central nervous system was involved, and to review the literature on this subject.

**Case Reports.** Case 1.—A white male, aged 5, on May 10, 1935, had a rash on his face and neck and a few swollen glands in his neck. He was not sick and went to school but was sent home on account of the rash. The family physician was called and a diagnosis of German measles was made. He advised the mother to keep the boy in the house for a few days. On May 13, while playing, he suddenly had a convulsion. The convulsive movements, which started on the right side and spread to the left side, lasted about 2 to 3 minutes. The patient was then unconscious for approximately 45 minutes. He had another convulsion on the night of May 14, and 2 more on the night of May 15.

On examination, on the morning of May 16, at this hospital, the patient was semistuporous. The temperature was 100° F. The head and eyes were deviated to the left. The pupils reacted normally to light and the optic fundi were normal. The right face, arm and leg were paralyzed. Visual fields could not be accurately tested, but the patient would not pay any attention to a light or other objects when presented in the right visual field, whereas he followed them readily in the left visual field. Psychomotor tests were unreliable. Spontaneous speech was absent, but he responded slowly to question. A few mistakes were made in naming objects placed before his eyes. Cutaneous sensation was apparently unimpaired. The knee jerks were absent, but the ankle jerks were present. The abdominal and cremasteric reflexes were absent on the right, but present on the left. The left plantar response was flexor in type and the right was questionably extensor in type.

*Laboratory Data.* The red blood count was 4,000,000; hemoglobin, 80%; white blood count, 7000. The urine was normal. Lumbar punctures performed on May 14 by Dr. Gorman showed that the cerebrospinal fluid pressure was normal. The fluid was clear, contained 50 lymphocytes

per c.mm. and the globulin test was positive. On May 15, the cerebrospinal fluid was under a pressure of 80 mm. of water. The fluid was clear and contained 16 lymphocytes per c.mm. The protein content was 37 mg., sugar, 50 mg., and chlorid, 646 mg. per 100 cc. The colloidal-gold curve was 0121100000, and the Wassermann reaction was negative.

*Course.* The patient improved rapidly and on the morning of May 17 was bright and alert. The conjugate deviation of the head and eyes had disappeared. Examination of the visual fields was normal and no disturbance of speech was detectable. The paralysis of the right side was improving, but a few clonic movements of right face and arm occurred at intervals throughout the day. Within the next few days the weakness of the right side rapidly disappeared. The knee jerks and the right abdominal and cremasteric reflexes returned. With disappearance of the paralysis a slight intention tremor developed in the right arm, which persisted for a few days. After 10 days the patient was allowed out of bed and played with toys and colored crayons without any evidence of weakness, tremor or awkwardness of the right arm or leg. He was kept in the hospital a few days longer because his sister had just developed German measles. Examination of the spinal fluid before discharge gave normal results. The fluid contained 2 cells, the protein content was 27 mg., sugar 60 mg., chlorid 720, and the colloidal-gold reaction negative.

Case 2.—(Dr. Putnam's Case.) A white housewife, aged 33, on May 24, 1935, became ill with a rash, swelling of the postcervical glands, vomiting and slight fever, which was diagnosed as German measles by her physician. She was sick for only 1 day. On May 27, 3 days after the outbreak of the rash, there was a return of the fever and vomiting accompanied by severe headache, dizziness and vomiting. The following day the speech became slurred. Examination at that time showed nystagmus and absent abdominal reflexes. On May 30, she complained of blurring of vision. She became disoriented and incoördination of the muscles was noted. On May 31, patient was in a curious uncoöperative state, usually sulky, but occasionally facetious. She was imperfectly oriented as to time, place and person and her memory was impaired. The nystagmus was still present and there was a slight weakness of the left side of the face. Movements of the arms were slightly incoördinated. The deep reflexes were normal, but the abdominal reflexes could not be obtained. Babinski's toe sign was present on the left side. There was no stiffness of the neck or Kernig's sign.

*Laboratory Data.* The red blood cell count was 5,000,000 and the white blood count 11,000 per c.mm. The cerebrospinal fluid removed by lumbar puncture on May 31 was under a pressure of 80 mm. of water. The fluid was clear and contained 5 lymphocytes per c.mm. The protein content was 82 mg.; the sugar, 73 mg. per 100 cc., and the colloidal-gold curve, 1123221100.

*Course.* The patient improved rapidly and was free of all symptoms within a few days. On examination 2 weeks later she was clear mentally, and the neurologic examination was negative except for absent abdominal reflexes and a questionably abnormal plantar response on the left side.

Case 3.—(Dr. Horrax' Case.) A white boy, aged 14, on May 14, 1935, developed a rash and swollen glands in the neck, which was diagnosed as German measles by the local physician. Two of his siblings were also sick at the same time with German measles. He remained in bed for 2 days and the rash disappeared. On May 20, 6 days after the onset of the rash, he began to complain of headaches and on the next day, after vomiting several times, lapsed into coma from which he recovered after a few minutes. On May 22, he had another vomiting spell and became unconscious for 2 hours. On May 23, he again became unconscious, with labored respira-

tions, and was brought to the New England Deaconess Hospital. On the way to the hospital he recovered consciousness and twitching movements of the head, left arm and left leg occurred. Immediately on entry to hospital he again became comatose, the respirations depressed and he appeared in a critical condition.

*Laboratory Data.* A lumbar puncture was immediately performed. The pressure was 400 mm. of water. The fluid was clear and contained 45 white cells per c.mm. The protein content was 60 mg.; sugar, 60 mg.; chlorid, 714 mg., and the colloidal-gold and Wassermann reactions were negative. There was immediate improvement in the patient's respirations, the cyanosis disappeared and convulsions did not recur.

*Course.* He continued to improve and within 24 hours was conscious and rational and remained so. Neurologic examination was negative except for a slight right facial weakness and inequality of the pupils. He remained in the hospital for 10 days and was discharged without any symptoms or abnormal signs.

CASE 4.—An Italian female, aged 9, was admitted to this hospital, July 10, 1935, in a semicomatose condition. The mother stated that the child had been perfectly well until July 6, when a rash appeared on the arm, which rapidly spread to involve neck, face and chest, accompanied by slight fever. The child did not feel ill, but was kept in the house for 2 days, by which time the rash had disappeared. On the morning of July 10, while playing in the yard, she suddenly fell to the ground unconscious. She arose after a few seconds, ran confusedly around the yard and began to beat her head against a stone wall. She was carried to her home in a rigid state, cyanotic and frothing at the mouth. The family physician was called and the patient was given a hypodermic injection, after which she became quiet. In the afternoon the patient awoke and became maniacal, thrashing about in the bed, screaming loudly and would not respond to questions or commands. She was then brought to the hospital.

Examination at that time showed in addition to the maniacal behavior, stiffness of the neck, Kernig's signs and bilateral Babinski's sign. The knee and ankle jerks could not be obtained and the abdominal reflexes were absent. The temperature was 103° F., pulse 130 and blood pressure 90/60.

*Laboratory Data.* The red blood count and hemoglobin content of the blood were normal. The white blood count was 15,000. The urine was normal. The cerebrospinal fluid removed at cistern puncture was under a pressure of 80 mm. of water, and contained 30 cells per c.mm., 75% of which were lymphocytes. The protein content was 79 mg.; sugar, 82 mg.; chlorid, 655 mg. per 100 cc., and the colloidal-gold curve, 0012321000. The blood and cerebrospinal fluid Wassermann reactions were negative.

*Course.* She became more confused and restless and refused to take fluids by mouth. The temperature rose to 105° F. about 8 hours after entry. Large doses of sedatives were given to quiet the patient and fluids were forced by catheter introduced into the esophagus through the nose. The child remained delirious for about 48 hours, gradually improving, and on July 13, the third day after admission, she was able to sit up in bed and talk rationally. The stiffness of the neck was still present, but the reflexes had all become normal. Ten days later the patient was discharged from the hospital with no residua.

We have been able to find 7 cases described in the literature.[1] These cases will be discussed in connection with our own. In addition to these 7, several other cases are mentioned. Benard[1a] reported that he has seen 12 cases of German measles with meningeal symptoms in which the cerebrospinal fluid contained excess cells.

He also quotes Sevestre as reporting the case of a young woman with delirium during an attack of German measles, Alliot as mentioning stiffness of the neck and conjugate deviation in 1 case, and Labougle as reporting the case of a soldier with fever, violent headaches, semicoma, and athetoid movements, with recovery. Siegl[1d] states that Freud and Rie cite several cases of hemiplegia after German measles in their monograph on infantile hemiplegia. These cases are not included in the discussion because the original reports were either inadequate or were not available to us.

**Discussion.** The signs and symptoms in the cases of encephalomyelitis following German measles (rubella) recorded in the literature and in those examined by us are the same as those described by Ford[2] in cases of measles (morbilli). In general, the cases may be divided into two groups according to the clinical symptoms indicating the portion of the central nervous system most severely involved: (1) Cerebral; (2) spinal cord, or brain stem. Meningeal symptoms, such as headache, stiffness of the neck and Kernig's sign may be present in either group or may occur as the only indication of involvement of the nervous system. The cases with cerebral involvement may show mental confusion, delirium, stupor, coma, convulsions, hemiplegia, or other focal signs. Those with spinal cord or brain-stem involvement show paraplegia, urinary retention, pyramidal tract signs, absent reflexes, diplopia, or cranial nerve palsies.

Table 1 gives a summary of the 7 cases reported in the literature and our 4 cases. These cases are analyzed more in detail below.

TABLE 1.—SUMMARY OF THE SYMPTOMS AND SIGNS IN 11 CASES OF ENCEPHALOMYELITIS FOLLOWING GERMAN MEASLES.

| Author. | Age. | Sex. | Days after onset of rash. | Headache. | Convulsions. | Stiff neck. | Neurologic signs. | Result. |
|---|---|---|---|---|---|---|---|---|
| Benard | .. | .. | 4 | 0 | 0 | 0 | Paraplegia; later bulbar paralysis | Died. |
| Debré | 7 | M | 2 | 0 | ++ | 0 | Coma; conjugate deviation to left | Recov. |
| Debré | 8 | M | 2 | + | ++ | 0 | Coma; mental symptoms | Recov. |
| Brock | 23 | F | 3 | ++ | 0 | + | Diplopia; urinary retention; Babinski | Recov. |
| Siegl | 9 | F | 4 | ++ | + | 0 | Mental confusion; bilateral Babinski | Recov. |
| Gennes | .. | .. | 5 | ++ | 0 | + | Mental confusion; urinary retention | Recov. |
| Skinner | 10 | M | 3 | 0 | + | 0 | Mental confusion; absent reflexes; Babinski | Recov. |
| Authors: Case 1 | 5 | M | 3 | 0 | ++ | + | Conj. dev. to left; right hemiplegia and hemianopsia; absent K. J.; cerebellar signs | Recov. |
| 2 | 33 | F | 3 | + | 0 | 0 | Mental confusion; nystagmus; left Babinski | Recov. |
| 3 | 14 | M | 6 | + | + | 0 | Coma; muscle twitchings | Recov. |
| 4 | 9 | F | 4 | 0 | + | + | Mental confusion; delirium; absent reflexes; bilateral Babinski | Recov. |

*Age and Sex.* The age varied between 5 and 33 years, with the great majority under 15. They are about equally divided between the 2 sexes.

*Time of Onset of Involvement of the Central Nervous System.* The interval between the appearance of the rash and the onset of neurologic symptoms in the 11 cases varied between 2 and 6 days, with an average of 4 days.

*Vital Signs.* The temperature is usually normal or only slightly increased with the onset of the involvement of the nervous system, but rarely it may be markedly elevated (103° to 105° F.), as in our Case 4. The respirations are usually not affected, but they may be markedly depressed, as in our Case 3.

*Neurologic Signs and Symptoms.* Headache was a presenting symptom in 6 of the 11 cases. Stiffness of the neck, or Kernig's sign, was found in 4 cases; attacks of unconsciousness with convulsive movements in 7 cases, mental confusion in 6, conjugate deviation of the head and eyes in 2, diplopia in 1, nystagmus in 1, hemiplegia and hemianopsia in 1, urinary retention in 2, paraplegia in 1, absent deep reflexes in 3, Babinski's toe sign in 5, cerebellar signs in 1 case and bulbar paralysis in 1.

TABLE 2.—THE CEREBROSPINAL FLUID FINDINGS IN 11 CASES OF ENCEPHALOMYELITIS FOLLOWING GERMAN MEASLES.

| Author. | Cerebrospinal fluid findings. | | | | |
|---|---|---|---|---|---|
| | Pressure, mm. of water. | Cells, per c.mm. | Protein, mg./100 cc. | Sugar, mg./100 cc. | Colloidal gold. |
| Benard | | * | | | |
| Debré: | | | | | |
| Case 1 | | 23 | 45 | | |
| Case 2 | | 400 | | | |
| Brock | | 296 | 70 | | |
| Siegl | | 33 | | | |
| Gennes | | 90 | 40 | 70 | |
| Skinner | | 13 | | | |
| Authors: | | | | | |
| Case 1 | 85 | 50 | 35 | 50 | 0121100000 |
| Case 2 | 80 | 5 | 82 | 73 | 1123221100 |
| Case 3 | 400 | 45 | 60 | 60 | 0000000000 |
| Case 4 | 60 | 30 | 79 | 82 | 0012321000 |

* Reported as increased. Number not given.

*Cerebrospinal Fluid.* The cerebrospinal fluid findings are summarized in Table 2. They are similar to those reported by Ford[2] in cases of measles encephalitis. The pressure is usually normal. Rarely it may be moderately or markedly increased (400 mm. in our Case 3). The cell count is increased, usually varying between 10 and 200 per c.mm. Rarely only a few cells are present or there may be several hundred cells per c.mm. (400 per c.mm. in Debre's Case 2). Lymphocytes are the predominating cell type, but a few neutrophils are usually present. The protein content is moderately increased. The sugar content is normal. The chlorid content is

normal or slightly decreased. The colloidal-gold reaction is normal or shows a midzone curve. The fluids are sterile.

*Pathology.* The pathology of encephalomyelitis following German measles has never been carefully studied. A necropsy was performed in Benard's case, but the histologic changes were not described. He merely states that there was an acute myelitis, disseminated over the entire cord. There is no reason to believe that the lesion in these cases is any different from that of measles encephalomyelitis as described by Greenfield,[3] and by Ferraro and Scheffer.[4] The etiology of the nervous involvement is not known. Similar pathologic changes have been reported in cases of encephalomyelitis following variola, vaccinia and other exanthemata. It has been suggested that possibly a filtrable virus may be the etiologic factor, but it is our feeling that the lesions can best be explained on the basis of vascular changes as suggested by Putnam.[5]

*Frequency.* We are unable to give any estimate as to the frequency of involvement of the central nervous system in cases of German measles. We are sure that the few cases reported in the literature do not represent a fair estimate of its occurrence, as most neurologists with a wide experience have encountered 1 or more cases. It is probable, however, that the frequency is less than the 0.4% as given by Ford for measles.[2]

*Diagnosis.* When the typical history of the onset of mental or neurologic symptoms 2 to 6 days after the rash is obtained there is usually no difficulty in the diagnosis. The cerebrospinal fluid findings serve to confirm the diagnosis. There has been doubt, however, in the minds of some clinicians concerning the validity of the diagnosis of German measles (rubella) in the cases that later develop encephalomyelitis, and they properly question whether these were not mild cases of measles (morbilli). The diagnosis in both of these exanthemata is a clinical one. Therefore we do not see the justification for making a retrospective change in the diagnosis in a typical case of German measles when neurologic symptoms develop.

*Prognosis.* There has not been a sufficient number of cases recorded in the literature to draw any definite conclusions in regard to the mortality or as to the ultimate outcome in the cases that live. Only 1 of the 11 cases shown in Table 1 died, which gives a mortality of 9%. This is approximately equal to that (10%) found by Ford[2] in measles encephalitis. Ford reported sequelæ in 65% of the cases of measles encephalitis divided as follows: residual weakness, 30%; ataxia, 12%; mentality defects or personality changes, 17%; epilepsy, 5%. While none of the cases of encephalomyelitis following German measles has shown any paralysis or ataxia, most of the cases recorded in the literature, as well as those observed by us, have not been followed long enough to determine whether mental defects, personality changes or epilepsy

may result. It is perhaps noteworthy that the disabling Parkinsonian syndrome, which is so frequently a sequel of epidemic encephalitis, has never been recorded in the post-measles or post-German measles encephalitis.

**Summary.** The clinical history and findings in 4 cases of encephalomyelitis following German measles (rubella) are reported. The literature on this subject is reviewed and these cases are compared to those that occur after measles (morbilli).

We wish to thank Dr. T. J. Putnam and Dr. G. Horrax for permission to report their cases.

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## OBSERVATIONS ON THE EFFECT OF MALARIA ON THE WASSERMANN REACTION.

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The occasion not infrequently arises in sections where malarial fever is prevalent when it becomes necessary to interpret a positive Wassermann reaction of the blood serum taken during the course of such an infection. The question as to whether or not malarial fever does cause such changes in the blood serum as may give false-positive serologic reactions has been much disputed, and has been the subject of many reports. Because of the inconclusiveness of the available literature and because of the importance of this question in the subsequent management of the patient, we have thought it worthwhile to review the experience of the Roper Hospital,

situated in a locality where both malaria and syphilis are common, in an attempt to throw further light on this disputed point.

While an extensive literature has accumulated regarding the influence of malarial fever on the Wassermann reaction, most reports deal with cases studied some years ago, in which only complement-fixation tests were performed, and before many of the newer serologic tests for syphilis had been developed. According to Lloyd and Mitra,[1] the opinion that malaria is responsible for non-specific positive reactions in certain cases originated largely from the address given to the British Medical Association by Wassermann in 1910. These authors have prepared an excellent summary of the more complete reports up to the time of their writing, from which they conclude that little reliance may be placed on many of the earlier observations because of faulty technique in the performance of the serologic tests and because of the inadequacy of precautions taken to exclude the possibility of syphilis. In their own cases, 85 in number, positive reactions were found in 14%, which they state falls easily within the expected syphilis rate of their hospital population in Calcutta. They conclude, therefore, that there is no evidence that malaria causes positive serologic reactions when modern techniques are carried out. A similar conclusion is reached by Thomson and Mills,[2] Iyengar,[3] Levy,[4] Johnson,[5] and Chambers.[6]

A diametrically opposite view is taken by other observers, many of whom maintain that at times malaria is a cause of false-positive serologic reactions. Craig[7] made this statement in a paper upon the complement-fixation test published in 1910, and repeated the opinion again in 1921.[8] St. John,[9] likewise, found non-specific reactions in 4.9% of a total of 101 cases of acute malaria. More recently, in the studies made for the evaluation of the serodiagnostic tests for syphilis in this country,[10] of 36 presumably non-syphilitic patients with malaria, positive serologic reactions were found in from 8.6 to 20.6%.

Confusion in regard to this question has arisen largely from two factors. In the first place, the results have been obtained over a period of years, using widely different modifications of the original complement-fixation technique, all of these being designated as the Wassermann reaction. It is of particular significance that most of the false-positive cases were reported in the early days of the complement-fixation test, and that with the modern advances in technique and in standardization, fewer non-specific positive reactions are being reported now than formerly. Secondly, because a definite history of primary infection is so often lacking, and because the physical signs of the latent stage of syphilis so often escape notice, the correct interpretation of a positive serologic reaction, obtained in the presence of another infection, is beset with difficulty. While it is surely safer to place more reliance on serologic than on

other evidence of syphilis, some observers seem to have erred in accepting the former with too much finality, and they are liable to almost as much criticism as those who dismiss the possibility of syphilis when a suggestive history or physical findings are not obtained. The middle road is indeed difficult to reach.

**Material and Results.** The present study is based on the case records of 262 patients, representing all of the cases of malarial fever admitted to the Roper Hospital during the years 1930 to 1934, inclusive, in which parasites were found in the blood smear and the serologic tests for syphilis were performed. Those cases were excluded in which the tentative diagnosis of malaria was made, based on clinical findings but unsupported by positive identification of parasites, as well as all cases in which serologic tests were not carried out. Throughout this period, the Kolmer modification (qualitative) of the complement-fixation test was used; in addition, during 1930 and 1931, the standard Kahn flocculation test was done routinely, while from 1932 to 1934, the Kline diagnostic test was carried out. The series of 262 patients includes 134 whites and 128 negroes. *P. vivax* was found in the blood smear in 159 instances, *P. falciparum* in 75, both types of parasites in 15, while in 13 cases positive differentiation between the two types was not made. In this group of patients, negative serologic tests were found 192 times (107 white, 85 negro), and positive results of varying degrees of strength in 70 cases (27 white, 43 negro).

In attempting to interpret the positive serologic findings in the group of 70 cases in which they occurred, a study was made of all relevant data that could be obtained: (1) A suggestive history of primary or secondary lesions of syphilis; (2) a history of previous specific treatment; (3) previous serologic tests; (4) subsequent serologic tests; (5) physical findings suggestive of syphilis, or findings compatible with that diagnosis, another explanation for which was not found. On the basis of these criteria, 23 cases were excluded as definitely syphilitic and 23 cases as probably syphilitic. In 9 cases adequate follow-up studies could not be made and these, therefore, were likewise excluded. Of the remaining cases, 15 in number, we believe 13 were definitely non-syphilitic and 2 possibly so in which the positive serologic tests were due to malaria; in none of these cases was there a history of any primary or secondary lesion, and in all physical examination disclosed none of the signs of a latent syphilitic infection. The essential findings in the first 12 cases of this false-positive group are noted in Table 1. None of these patients received antisyphilitic treatment, either before or during their attack of malaria, or afterwards in the interval between serologic tests.

One additional case seems worthy of more detailed consideration. The patient, a white man, aged 26, was admitted to the hospital on June 28, 1934, with a story of fever of 3 days' duration, and nausea and vomiting. Slight rigidity of the neck, noted early the

next morning, led to lumbar puncture. The findings in this and in the subsequent spinal fluid examinations, along with the results of the serologic tests on the blood serum, are noted in Table 2. The patient remained afebrile for several days after admission, but the fever returned, and on July 10 malarial organisms of the tertian type were found in the blood smear. Treatment with quinin was begun, the serologic tests on July 16 being done after 75 grains of the drug had been given. Neither during the patient's stay in the hospital nor at subsequent examinations were any physical or neurologic signs noted to substantiate a possible diagnosis of syphilitic involvement of the central nervous system.

TABLE 1.—PATIENTS WITH FALSE-POSITIVE WASSERMANN REACTIONS DUE TO MALARIA.

| No. | Color. | Age, yrs. | Type of infection. | Therapy before serologic test, gr. | Temp. at time blood taken. | Serologic test. | Date. | Repeat serologic test. | Date. | Repeat serologic test. | Date, 1935. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | W | 19 | T | Q 25<br>P ½ | 102 | W 0<br>K + + | 11-6-32 | W 0<br>K 0 | 11-16-33 | W 0<br>K 0 | 1-19 |
| 2 | W | 27 | T | Q 70 | 100.6 | W + +<br>K + | 9-18-33 | W 0<br>K 0 | 12-15-34 | | |
| 3 | W | 14 | T | None | 99 | W +<br>K + + | 11-6-33 | W 0<br>K 0 | 11-23-33 | W 0<br>K 0 | 2-3 |
| 4 | W | 30 | T | Q 75<br>A 12 | 99 | W + + + +<br>K + + + + | 11-13-33<br>11-16-33 | W 0<br>K 0 | 8-29-34 | W 0<br>K 0 | 1-19 |
| 5 | C | 25 | T | Q 20 | 98.6 | W + + + +<br>K 0 | 12-13-34 | W 0<br>K 0 | 1-27-35 | | |
| 6 | W | 34 | T | Q 60 | 99 | W + +<br>K + + | 10-2-33 | W 0<br>K 0 | 3-14-35 | W 0<br>K 0 | 7-24 |
| 7 | C | 3 | T | A 9 | 99.4 | W + + +<br>K + | 9-6-34 | W 0<br>K 0 | 1-27-35 | | |
| 8 | C | 15 | T | A 3 | 104 | W 0<br>K + + | 7-23-34 | W 0<br>K + | 7-30-34 | W 0<br>K 0 | 3-26 |
| 9 | W | 7 | EA | A 12<br>P 1½ | 99 | W + +<br>K 0 | 11-13-33 | W 0<br>K 0 | 1-24-35 | | |
| 10 | W | 25 | EA | Q 40 | 101 | W + + +<br>K 0 | 8-6-34 | W 0<br>K 0 | 8-20-34 | W 0<br>K 0 | 1-14 |
| 11 | C | 14 | EA | None | 101 | W + + + +<br>K 0 | 8-30-34 | W + +<br>K 0 | 9-6-34 | W 0<br>K 0 | 1-27 |
| 12 | W | 11 | M | A 7½<br>P 3/6 | 100 | W + + +<br>K 0 | 11-13-34 | W 0<br>K 0 | 11-16-34 | | |

Abbreviations: T = Tertian; EA = Estivo-autumnal; M = Mixed; Q = quinin sulph.; A = Atebrin; P = Plasmochin; W = Kolmer test; K = Kline test.

TABLE 2.—CASE WITH FALSE-POSITIVE SPINAL FLUID WASSERMANN REACTION.

| Date: | 6-29. | 7-2. | 7-9. | 7-16. | Nov. | Jan. |
|---|---|---|---|---|---|---|
| Spinal fluid serology | W + + + +<br>K 0 | .. | W 0<br>K 0 | W 0<br>K 0 | | |
| Spinal fluid cell count | 4 | .. | .. | 5 | | |
| Blood serology | .. | W 0<br>K 0 | .. | W + +<br>K 0 | W 0<br>K 0 | W 0<br>K 0 |
| Temperature | Nor. | Nor. | 100° | 99° | Nor. | Nor. |

W = Kolmer test. K = Kline test.

**Discussion.** From the evidence at hand, it would seem that in all of the above cases the positive serologic tests were non-specific. While historic methods are notoriously inadequate and while the physical signs of a latent syphilitic infection are often minimal and difficult to elicit, in the absence of both of these indications the diagnosis of syphilis cannot be sustained when the sole basis for the latter has been a weakly positive serologic test. And this is especially true when the serologic reaction becomes and remains negative without any specific treatment whatsoever. In the group of 13 false-positive cases, there was agreement between the Kolmer and Kline tests in 5 cases and complete disagreement in 8; of the latter, the Kline test remained negative in 6, the Kolmer test in 2. In the 3 cases of estivo-autumnal malaria and the case of mixed infection, the Kline test was negative. The temperature at the time the blood was taken for serologic tests seemed to have made no difference in the results, being under 100° F. in 7 cases, and over 100° F. in only 6. The kind and amount of treatment prior to the test was likewise inconsequential in the results obtained. In the group of 193 sero-negative cases, which may be used as controls, the temperature ranged from normal to 106° F., and the amount and kind of treatment before testing was also sufficiently varied as to serve as an adequate control for this possible factor.

Whether or not the positive spinal fluid complement-fixation test in Case 13 (Table 2) can be considered as a non-specific reaction due to malaria is debatable. This condition has not been previously reported, but it is not surprising in view of the fact that the occasion for lumbar puncture does not arise very frequently in patients with malaria. In this case, while the patient was undoubtedly infected with malaria at the time the test was performed, parasites were absent from the peripheral blood and there was no fever. The temperature did not begin to rise again until about 1 week later, after which time tertian organisms were definitely identified. However, no other possible explanation for this false-positive result can be advanced, and it is reported here as being possibly due to malaria. In 7 other cases in which spinal fluid examination was made, the results were negative in 5, and positive in 2 known syphilitic patients.

Statistical analysis shows that in the entire group of 262 patients, positive serologic tests were found in 20.1% of the white patients and 33% of the negro. The normal syphilis rate for this community was studied some years ago by Johnson,[11] whose reported that in 30,000 serologic tests, 15% were positive in white patients, 45% in negro. The discrepancy between these figures and the percentages found in the group of malarial cases probably lies in the fact that almost half of the negro patients in the malaria group were under 12 years, whereas in the general hospital population, children account for a much smaller percentage of admissions. If the adult negro patients are considered alone, 48.5% gave positive serologic

results, a figure close to the expected average. Excluding the definitely and possibly syphilitic patients, false-positive results were found in 6.3%.

Two additional cases remain for brief consideration. In the first, a white woman, aged 38, with estivo-autumnal malaria, strongly positive Kolmer and Kline tests were found and the patient was given a single injection of neoarsphenamin, 0.3 gm. Serologic tests repeated 1 month later showed the Kolmer reaction negative, the Kline test 2+. Subsequent tests, 1 and 2 months later, were negative by both methods. The temperature was elevated (101° F.) and parasites were present in the blood at the time the first tests were made. The second case was very similar, save that here the patient received 9 injections of neoarsphenamin, a total of 5.1 gm.; serologic tests became negative and had remained so 1½ years later. Both of these cases illustrate the difficulty in the subsequent management of the patient when antisyphilitic treatment is begun without sufficient clinical justification. It is easily possible that the second patient noted above had syphilis as well as malaria, but it is unlikely in the first case that a single injection of neoarsphenamin would be sufficient to cause the serologic reaction to revert to negative, if the latter were due to syphilis. However, because these 2 patients received specific treatment for syphilis, we have not felt justified in including either in the group of false-positive reactions due to malaria.

We have in no way attempted to ascertain the cause for the appearance of these non-specific positive serologic reactions which occur during the course of malarial fever. The mere fact of increased temperature has been assumed to be the cause of such false-positive reactions by some authors,[12] who state that negative results are obtained after the temperature has become normal. Kolmer[13] has emphasized the fact that acute febrile diseases may render the blood serum temporarily more anticomplementary, making it necessary to guard against non-specific reactions, but obtained no positive results in 11 cases of malaria. However, in the group of 36 cases of malaria tested recently by this method,[10] 19.4% positive reactions were found. In our own cases, we have not found that the temperature made any difference in the specificity of the results obtained. The therapeutic agents used in the treatment of malaria have likewise been eliminated as possible etiologic factors. The presence of malarial parasites in the peripheral blood stream has also been cited as a cause;[12] we have not examined the blood with sufficient frequency to determine whether or not parasites were demonstrable on the days on which the tests in our cases were taken, but judging by the amount of treatment that some of the patients had had, it is unlikely that this factor could have been responsible for all. An individual idiosyncrasy of some nature is possible, but 2 of the patients in our false-positive group were observed in recurrent attacks of malaria 1 and 2 years following their original attack,

at which times the serologic tests remained negative. The most recent suggestion as to the cause for the occurrence of these non-specific reactions has been made by Fischer and Günsberger,[14] who claim that the positive serologic reaction is traceable to the presence of antibodies directed specifically against erythrocytic lipoids liberated by the action of the malarial parasites on the red blood cells. These authors describe an extract of beef heart, relatively poor in these lipoids, which generally does not react with serum from malarial patients or reacts only weakly, although it is an excellent antigen for the test for syphilis. They state that the Wassermann reaction carried out simultaneously with the erythrocytic reaction can distinguish Wassermann-positive malaria from syphilis.

**Summary**. Because of the controversial nature of the literature in regard to the influence of malarial fever on the Wassermann reaction, we have examined the case records of 262 patients with malaria. Excluding those cases in which there was any suggestion of the possibility of syphilitic infection, non-specific positive serologic results were found in 6.3%.

One case is reported in which the spinal fluid complement-fixation test was positive, most probably a non-specific reaction due to malarial infection.

The authors wish to express appreciation to Dr. Francis B. Johnson and the members of his laboratory staff for their assistance and suggestions in this study.

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# COLLAPSE THERAPY FOR TUBERCULOSIS IN THE SMALL SANATORIUM

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When this sanatorium was opened, in 1931, the extensive use of collapse therapy was, with rare exceptions, restricted to large sanatoria and other tuberculosis centers. Being convinced that collapse therapy was as essential for good results in a small sanatorium as in a large one, we determined to give our patients the benefit of this therapy whenever indicated. The results of this program, from every point of view, have been so satisfactory that we feel that our experience should be reported briefly.

The Jackson County Sanatorium has a capacity of 58 adult patients. The medical staff consists of only one physician, who also conducts the out-patient department and administers the business affairs of the institution. He carries out all pneumothorax treatments. At a distance of 35 miles there is an experienced thoracic surgeon who is consultant of the sanatorium. He visits the sanatorium at frequent intervals for a medico-surgical consultation. He performs only the phrenic nerve operations at the institution; more extensive operative procedures are performed at his hospital where the patients may be under constant surgical supervision during their immediate postoperative convalescence.

The ensuing study covers the period from January 6, 1931, to September 1, 1934.

The National Tuberculosis Association has recently published average results based upon a survey[1] of all civilian sanatoria in the United States in 1931. It is well known that the percentage of use of collapse therapy in the country as a whole in 1931 was relatively low. Seventeen per cent of the patients in their report were discharged as arrested or apparently arrested,* 41% as quiescent or improved, 19% as unimproved and 23% as dead. One hundred and nine patients have been discharged from this sanatorium, where 48% have received collapse therapy, with the following results: 55% arrested or apparently arrested, 25.8% quiescent or improved, 0.9% unimproved and 18.3% dead.

The National Tuberculosis Association figures show that 49% of the patients were in the far-advanced stage of tuberculosis upon admission, 28% moderately advanced and 15% minimal. The corresponding figures for the Jackson County Sanatorium concerning 157 admissions are 59.2%, 28%, and 12.8%, respectively.

The contrast between the foregoing discharge results is even more

* The stage of the disease and the results are classified according to the criteria of the National Tuberculosis Association.

striking if the fact be accepted that the great majority of the patients who were unimproved, and a considerable proportion of those classified as improved and quiescent, will probably die. Nineteen per cent of the patients in the National Tuberculosis Association report were classified as improved upon discharge and an additional 23% were dead upon discharge, a total of 42%. Only 0.9% of our patients were unimproved upon discharge and 18.3% were dead, a total of 19.2%. The sum of the dead, unimproved, improved and quiescent in the National Tuberculosis Association report is 83%, and in our report only 45%. Only 17% of the National Tuberculosis Association patients had arrested tuberculosis, whereas 55% of ours had. Still further significance may be attached to the comparative results when it is revealed that 45% of those dying in our group were too ill to be considered for collapse therapy—this giving a death rate of but 10% among all patients considered upon admittance as having any possible opportunity of recovery. Incidentally, we have made no attempt to select favorable cases for admission; this is illustrated by the fact that 59.2% had far-advanced tuberculosis upon admission, whereas only 49% of the patients admitted to all civilian sanatoria in the United States in 1931 had far-advanced disease.

We have used collapse therapy on every patient for whom we felt that it was strongly indicated. In some of our minimal and moderately-advanced cases and in a few far-advanced cases we did not use collapse therapy because we felt that their chances of recovery without it were good and our limited financial resources at the time required that we should reduce expenditures to the minimum. Nevertheless, we believe that temporary phrenic paralysis or pneumothorax should be used even for those cases who may recover without collapse therapy, for the reason that these measures, when properly used, definitely increase the chances of recovery and hasten it.

Collapse therapy has been used upon entrance in only 5% of our minimal cases, in 50% of our moderately-advanced cases, and in 56.9% of our far-advanced cases: an average total of 48.4%. It is interesting that 36% of our far-advanced were admitted to the sanatorium in such poor condition that no collapse therapy could reasonably be considered.

During the $3\frac{3}{4}$ years, 109 of the 157 patients with the adult type of pulmonary tuberculosis who have been admitted to the sanatorium have been discharged. The 109 patients do not include 16 who left, against medical advice, less than 3 months after admission, or who entered the sanatorium within 3 months of the preparation of this report. These patients are excluded because they obviously are unsuitable to illustrate the effect of treatment.

The results upon discharge of the 109 patients in whom the results of a fair trial of treatment are known appear in Table 1.

TABLE 1.—RESULTS AT TIME OF DISCHARGE (109 PATIENTS).

| Classification at admittance. | Arrested or apparently arrested. | | Quiescent. | | Improved. | | Unimproved or worse. | | Died. | | Total. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | %. | No. | %. | No. | %. | No. | %. | No. | %. | No. | %. |
| Minimal | 14 | 93.3 | 0 | 0.0 | 1 | 6.7 | 0 | 0.0 | 0 | 0.0 | 15 | 100.0 |
| Moderately advanced | 24 | 72.8 | 6 | 18.1 | 2 | 6.1 | 0 | 0.0 | 1 | 3.0 | 33 | 100.0 |
| Far advanced | 22 | 36.0 | 9 | 14.8 | 10 | 16.4 | 1 | 1.6 | 19 | 31.2 | 61 | 100.0 |
| Total | 60 | 55.0 | 15 | 13.8 | 13 | 12.0 | 1 | 0.9 | 20 | 18.3 | 109 | 100.0 |

Whitney and Myers[2] reviewed the results of nearly 7000 cases discharged from two state sanatoria, one in an eastern industrial state and one in a southern agricultural state. They report 39% of the far-advanced cases as having died by the end of the first year and 52% by the end of the second year. After excluding patients leaving against medical advice after hospitalization of more than 3 months, and excluding transfers to other institutions, we have been able to follow 70 patients who have been voluntarily discharged by us within from 3 years to 3 months and find 95.8% still well, with no deaths. The tuberculosis in 3 (4.2%) became reactivated; these 3 patients, who had not previously had collapse therapy, returned to the sanatorium and have had collapse therapy.

An additional analysis of the group of 70 patients followed after discharge revealed that in the minimal group 6.6% had a positive sputum on entrance, none had cavitation; in the moderately-advanced group 39.2% had positive sputum and 24.1% had cavitation; in the far-advanced group 92.2% had positive sputum and 74% had cavitation. Upon discharge none of these patients had either a positive sputum or a cavity.

In view of the fact that we have used collapse therapy for the patient whose prognosis was obviously poor without it, it would be futile to compare the results of those patients who received collapse therapy with those who received only the unaided sanatorium regimen.

It is interesting, however, to note the results that have occurred in 26 cases who left the sanatorium against medical advice at some time before their treatment was completed. Of this number, 7.6% are improved, while 92.4% are unimproved, worse or dead (28% dead). It is significant that 38% of the group that did badly reëntered the sanatorium for treatment and none has died; collapse therapy has been instituted in all cases.

**Conclusion.** A rather extensive use of collapse therapy, in connection with the sanatorium regimen, tremendously improves the

results of the unaided sanatorium regimen. It is hoped that this report may stimulate a greater interest in collapse therapy in small sanatoria, as well as in large ones.

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## PUNCH-DRUNK.

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There is a clinical syndrome of frequent occurrence among boxers, to which they refer as "punch-drunk," "punchy," "goofy," "slap happy," "cutting paper dolls," or "slug nutty." Other terms might be applied, such as "traumatic dementia" or "traumatic encephalopathy," but they are not nearly so appropriate and descriptive as the epithet "punch-drunk." The above terms were always somewhat familiar to me, and with the development of a medical viewpoint, I wondered if there really existed a traumatic dementia, such as indicated by these names, or if they were misnomers charitably denoting a traumatic origin to an incidental mental abnormality. The impetus to investigate this question and, if possible, to add to the original description of this condition given by Martland,[1] in 1928, came with the necessity of preparing a thesis for graduation.

I determined to study "punch-drunk" in its natural habitat, the boxing world. Accordingly, I frequented training quarters, helped examine fighters, and made friends with all sorts of "pugs." I observed declining veterans of the ring, talked with their trainers, and drank beer with their managers. I interviewed sports writers, referees and boxing commission physicians. I sought out reputed "punch-drunks" and studied them to the fullest extent that their feeling of exuberant good health would permit of a medical examination. My knowledge of the subject, then, is based upon the information given me by laymen whose business is a keen study of boxers, and the incomplete observation, over a period of 2 years, of many cases of "punch-drunk."

The course of a typical case is somewhat as follows: A sturdy young man trains in a gymnasium as an amateur boxer in order that he may develop himself physically, and master the finer points of pugilism. He becomes a fairly tough opponent in the ring, but he tends to fight rather than box, and so receives some degree of

punishment in each of his 30 or 40 short amateur matches. Later, he becomes a professional, meets stiffer opposition, engages in longer fights; but he is young, strong, and is "making good money." After a period of approximately 4 years as a professional boxer, during which time he has engaged in about 30 to 60 bouts, he begins to "soften up." His tolerance to all head blows is reduced. After being struck on the jaw, he remains dazed for a longer period than formerly, and is more likely to be knocked out ("glass jaw"). After a blow to the head, his legs will be a little shaky, and feel numb. His timing begins to fail and the fighter is no longer as dangerous on offensive as he had been. His defensive, which had been steadily improving with each encounter, becomes also less effective, and the pugilist who previously had been adroit enough to go through a career unmarked now begins to develop a flat nose and cauliflower ears. Later his knees tend to give way after a head blow, and a slight dragging of the feet may be noticed, although often only as the contestant is walking to his corner at the end of a round. The fighter still boasts of feeling fine and capable, but now loses engagements which formerly he could have won with ease.

Meanwhile the boxer's manager and associates begin to notice changes in him. They find that he has developed deterioration in attention, concentration and memory. In the midst of a conversation he may go into a reverie, suddenly change the subject, or ask the same question several times. He is apt to become too sociable, and very voluble. Usually an impediment of speech will develop, and the eyes may become slightly glazed or have a staring expression ("glass eye"). In short, he may continuously simulate a person who is just a little drunk. When these symptoms have once appeared, they will not only persist, but may progress for a period of a year or so when they will usually become stationary. Thus punch-drunk is a self limited rather than a progressive encephalopathy.

In the severer cases, the voice may become thick, halting and guttural, as though there were something held in the mouth. The gait may become unsteady. In a few instances vision may begin to fail or some degree of deafness may appear. Headache, dizziness and tinnitus, which one might expect as symptoms, are often present for a few hours or days following a fight, but they rarely persist as a part of the syndrome. Mental and personality changes become more marked, and emotional instability becomes apparent. Involuntary habit movements of a boxing nature are common, and are frequently displayed, even years later, when the person is abstractly preoccupied or during periods of emotional stress. A punch-drunk, sitting as a spectator at a fight, may vigorously ape the blows of his friend in the ring, oblivious to the other people about him. Punch-drunks almost universally do not realize that there is anything abnormal about themselves or their conduct, and

will hotly resent, often with their fists, any application of this stigma to themselves.

The more intelligent boxers are alert to recognize even early manifestations, and from the beginning plan retirement from active competition in the ring when ominous signs and symptoms first appear. The incident which precipitated Gene Tunney's decision to retire occurred during training for the second Dempsey fight. Tunney writes, "I went into a clinch with my head down, something I never do. I plunged forward, and my partner's head came up and butted me over the left eye, cutting and dazing me badly. Then he stepped back and swung his right against my jaw with every bit of his power. It landed flush and stiffened me where I stood. Without going down or staggering I lost all consciousness of what I was doing, and instinctively proceeded to knock him out. Another sparring partner, Eddie Eagan, entered the ring; we boxed three rounds. I have no recollection of this, nor have I any recollection of anything that occurred until the next morning when I awakened, wondering who I was and what I was doing there." For the next 3 days, Tunney was dazed and disoriented. He continues, "From that incident was born my desire to quit the ring forever, the first opportunity that presented itself. But most of all I wanted to leave the game that had threatened my sanity before I met with an accident in a real fight with 6-ounce gloves that would permanently hurt my brain. The possibility of becoming punch-drunk haunted me for weeks."[4] But the majority of boxers do not have this insight. They will continue to fight until they become so ineffectual in the ring that the promoters refuse to book them for any further matches. Some fighters, usually from economic necessity, will then enlist as sparring partners and receive further punishment while assisting in the training of others.

The type of boxer is a large factor in the likelihood of punch-drunk developing. It is most often seen in the wide-open slugging type of fighter who is out to give as much as he can, and thus usually takes quite a lot in return. It is rarer in cleverer boxers except after an extraordinarily long period in the ring. They rely on speed and coördination rather than strength. Such men usually have good defenses, and receive less punishment than cruder fighters, but they also seem less able to "take it." What would be a knock-out blow to their more highly developed nervous systems might be taken without much apparent damage by one of the brute type. The decline of the skilled boxer, when it finally comes, is often acute, and a single severe beating may result in marked decrease in fighting ability. This deterioration is chiefly in loss of speed and coördination. In the cruder boxers, speed and coördination have not been such important factors, and they continue along

on their "punch" after their finer control is lost, suffering many beatings before they are finally "through."

With reference to the incidence of punch-drunk, competent followers of the sport estimate that about 5% of men who remain in the professional ranks for a period of 5 years or more will become definitely punch-drunk. About 60% of fighters remaining in the ring for this period will develop mental and emotional changes which are obvious to people who knew them previously. A few deteriorate to the extent that institutionalization is necessary. Punch-drunk is said to occur among professional football players also.

In punch-drunk the prominence of objective mental changes and the freedom from symptoms are in contrast to the post-concussion syndrome in which subjective complaints are prominent, and objective mental changes are not often seen. In a survey of cases of gross brain traumas showing sequelæ, Glaser and Shafer found that over 80% were troubled by subjective symptoms, usually headache and dizziness, while "mental changes, consisting in disorders of the mental faculties with changes in character and habits, and associated with unreasonable and purposeless action and language" appeared in 9%, usually at an interval of months after the injury.[5]

Little information is available concerning the actual anatomic changes in punch-drunk. The explanation of this syndrome must be based on analogy and conjecture. Even the pathology of the common concussion is still disputed, although extensive clinical and laboratory studies have been made on this syndrome. Many authors have abandoned the stand that concussion is a transient disturbance of function without anatomic basis, and believe that it depends upon a permanent change resulting from multiple punctate hemorrhages through the brain substance.[6–10] These hemorrhages fill the perivascular spaces and, if large, infiltrate the surrounding nervous tissue. The neurones in the areas of these hemorrhages are damaged with subsequent degeneration. Organization and gliosis follow, with ultimate resorption of the glia cells and contraction of the glia fibers. This destruction of white and gray matter eventually results in shrunken convolutions, widened gyri, dilated ventricles and an enlarged subarachnoid space, with increase in the amount of cerebrospinal fluid. Small hemorrhages in the subarachnoid space are followed by local reactions, and subsequent pial-cortical adhesions.[9] Fay regards the decreased size of the brain in post-concussion cases as a result of pressure atrophy following deficient cerebrospinal fluid absorption.[11] Others believe it to be due to an increased production of fluid.[12] Some later writers have pointed out the similarity of this pathologic process to that seen in encephalitis, and have referred to it as "traumatic encephalitis." Clinical studies show much resemblance between post-concussion cases and some cases of encephalitis. Enceph-

alography in these post-concussion cases reveals extensive cortical or cerebral atrophy, external and internal hydrocephalus, and arachnoiditis, with obstruction to various cerebrospinal fluid pathways.[10, 11, 13] Of two encephalograms made on cases of punch-drunk under my observation, one showed no demonstrable changes. The other revealed definite cortical atrophy, which was localized to the left frontal region, rather than being diffuse in distribution. Since the injection of air into the subarachnoid space for encephalography relieves the subjective symptoms in about one-half of post-concussion cases, it is believed that the complaints are due to the arachnoiditis rather than to other pathologic changes. The absence of distressing local symptoms in punch-drunk is evidence against the presence of arachnoiditis.

Although multiple punctate hemorrhages probably constitute the underlying pathologic change in punch-drunk, extensive degeneration might be explained even without reference to such vascular lesions. It is hardly possible that a blow which jars the brain sufficiently to cause loss of consciousness would not be followed by some tissue reaction, such as hyperemia and edema with effusion into the intracellular spaces, leading to disturbances of nutrition and thus to impairment of function. An area with anatomic predilection to this type of injury is the midbrain. With a jar of the skull, the midbrain is forced against the sharp edge of the tentorium and bruised, resulting in edema and hyperemia. Following repeated insults to this region a gliosis may begin, and increase with each succeeding trauma. This scarring could result in a narrowing of the aqueduct, predisposing to the formation of an internal hydrocephalus with an increase in the intraventricular pressure and subsequent damage to the cortex.

Another explanation is that the jarring of the brain by a blow results in the fracturing of cell processes. The unequal specific gravities of the gray and white matter give to them different degrees of acceleration in response to a force. This inequality of movement might cause a rupture of the neurones at the junction of the two tissues.[14] The technical problems of demonstrating such minute lesions and differentiating them from artefacts leaves this occurrence unproven. The theory that functional changes may be based on a molecular disturbance or direct mechanical effect in the structural equilibrium of the cell likewise finds basis in the fact that protoplasm is an emulsoid containing lipoids, large protein molecules, and electrolytes in a watery base, and that these materials, having different specific gravities, will assume new relative positions in response to a violent movement, so that the cell cannot function normally.[15, 16]

However, the bizarre nondescript clinical picture seen in punch-drunk can probably best be explained on the basis of the small discrete vascular lesions which have been described. After pre-

senting a detailed neurologic analysis of 3 cases of punch-drunk, each having advanced physical disability, Parker summarizes, "The clinical picture in each case was very complex and it differed in one case from the others. The only agreement, however, was in the suggestion of diffuse or scattered lesions of the brain affecting different systems at one and the same time."[2] Jokl and Guttmann[3] conclude their paper on neuro-psychiatric studies on boxers with, "There are found organic symptoms which appear to the layman as dementia. A study reveals in many such cases various focal symptoms, reflex differences, disturbances in coördination and speech anomalies."

**Comment.** It is probable that no head blow is taken with impunity, and that each knock-out causes definite and irreparable damage. If such trauma is repeated for a long enough period, it is inevitable that nerve cell insufficiency will develop ultimately, and the individual will become punch-drunk.

The cognizance and investigation of this condition by the medical profession would be a contribution to the neurologic and psychiatric study of traumatic disorders. But a higher end would be the education of the layman to the remote dangers incident to repeated minor head traumas. The occurrence of this type of degenerative brain change must be recognized and publicized rather than disregarded and discounted. It is especially important that athletes entering into competitions in which head injuries are frequent and knock-outs are common should realize that they are exposing themselves not only to immediate injury, but also to remote and more sinister effects.

**Summary.** The clinical syndrome of punch-drunk is delineated by presenting a typical composite case study. The etiology and incidence are discussed, and the pathology is suggested.

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## THE RECOVERY OF BRUCELLA ABORTUS FROM THE STOOLS OF HEALTHY CARRIERS.

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Brucella abortus can be recovered from the stools of a certain number of cases of undulant fever. Leavell, Poston and Amoss[1] observed, in a small number of carefully studied patients, that the organisms persist in the stools of chronic and recurring types of abortus infection. In the past $2\frac{1}{2}$ years, in the Strong Memorial and Rochester Municipal Hospitals, the stools from 7 patients with this disease were cultured by a modification of the technique described by Amoss and Poston.[2] From four of these stools, brucella organisms were recovered.

The purpose of this study was to determine whether Br. abortus could be recovered from the stools of apparently healthy individuals, or from the stools of patients suffering from diseases other than clinically recognizable undulant fever, and also to describe a modification of the Amoss and Poston technique for the isolation of Br. abortus from stools. This method substitutes guinea pig inoculation for plate inoculation.

**Material and Method** *Material.* At the time that this investigation was planned, two studies were in progress which aided materially in the selection of suitable cases for study. All samples of blood, submitted to the Rochester Health Bureau Laboratories for the Wassermann test, were examined for abortus agglutinins. Simul-

taneously, intradermal tests with an abortus antigen were being made on a group of unselected patients. These studies made it possible to pick out a number of patients without clinical evidence of undulant fever, but with laboratory findings specifically indicative of Br. abortus infection.

Stools were obtained from 219 patients grouped as follows:

GROUP 1. Three hundred and thirty-two unselected hospital patients were tested for cutaneous reaction to an antigen prepared from Br. abortus No. 80. The organism was grown on liver infusion agar for 96 hours, after which the growth was removed and twice washed with physiologic saline. The bacterial suspension was centrifuged and, after discarding the supernatant fluid, the sediment was frozen and dried *in vacuo*. The dry material was then ground in a ball mill for 8 weeks. To the dry powder so obtained, physiologic saline was added and the grinding continued for 48 hours, this time in the icebox. The resulting suspension was filtered through a Berkefeld N candle. The final water-clear filtrate contained 13.3 mg. of nitrogen per 100 cc. It was standardized by repeated skin tests on a number of recovered cases of undulant fever and on several individuals with known sensitivity to abortus antigens, but with no clinical history of the disease. It was found that 0.1 cc. of 1 to 100 dilution of the filtrate gave a distinct erythematous reaction, without local necrosis and without the constitutional effects encountered with other antigens.[3, 4, 5]

Thirty-four (10.1%) of the 332 patients tested with the above described antigen gave positive cutaneous reactions. This percentage compares favorably with the number of reactors in this community previously determined with other antigens.[5]

From this group of 332 patients, stools were examined from each of the 34 patients who had a positive skin reaction and from 22 patients who gave negative reactions.

GROUP 2. Stools were collected from 139 patients whose sera had been tested for abortus agglutinins. Thirty-eight of these patients had anti-abortus agglutinins in their sera. Only 6 of the latter group were tested for cutaneous reactions. All were definitely positive.

TABLE 1.—AGGLUTININ TITERS FOR BR. ABORTUS OF 38 PATIENTS FROM WHOM STOOLS WERE AVAILABLE.

| No. of patients. | Titer. |
|---|---|
| 8 | 1 to 60 |
| 8 | 1 to 80 |
| 11 | 1 to 160 |
| 3 | 1 to 320 |
| 4 | 1 to 640 |
| 2 | 1 to 1280 |
| 2 | 1 to 2560 |

The sera from the remaining 101 patients in this series contained no abortus agglutinins.

GROUP 3. Stools were obtained from 24 patients whose sera were not examined for Br. abortus agglutinins, on whom skin tests were not performed and concerning whom no information of a possible abortus infection is available.

*Method of Stool Examination.* From 2 to 4 gm. of a fresh stool specimen were emulsified in 50 cc. of physiologic saline solution. This suspension was centrifuged at a low speed to remove the coarse particles. To the decanted fluid was added 0.5 cc. of an anti-abortus serum with an average titer of 1 to 640. The tubes were then incubated in a water bath at 37° C. for 2 hours, and again centrifuged at low speed for 5 minutes. After discarding the supernatant fluid, the sediment was emulsified in 2 or 3 cc. of physiologic saline and 0.25 cc. injected subcutaneously into each groin of a guinea pig. In all, 379 guinea pigs were inoculated. Pairs of animals were inoculated from each of 160 stools, while only one animal was used for each of the remaining 59 samples. From 25 to 35 days after inoculation, the guinea pigs were etherized, bled from the heart, and examined postmortem for evidence of abortus infection. The sera were examined for abortus agglutinins, using a saline suspension of living Br. abortus No. 80 as the antigen. The spleens were removed aseptically and cultured by planting pieces of tissue from 3 to 5 mm. in diameter on glucose ascitic blood agar. The cultures were incubated in an atmosphere of 10% $CO_2$ at 37° C. for 10 days.

To check the dependability of this method for recovering Br. abortus from stool emulsions, 5 stools, to which a few drops of a living abortus culture had been added, were included in this series. In each case Br. abortus was recovered from the animals.

Certain stool specimens were stored in the icebox for from 12 to 36 hours before examination. The viability of Br. abortus in human excrement under such conditions not being known, it was studied as follows. A few drops of a living abortus culture (No. 80) were thoroughly stirred into a normal stool and stored in a pint fruit jar in the icebox at 8° C. Guinea pigs were injected with specimens from this stool, prepared according to the above technique, on the 2d, 6th, 19th, 64th and 150th days after storage. Br. abortus was recovered in each instance. Cameron[6] has similarly found that Br. abortus survives for long periods in cow manure.

RESULTS. Organisms of the genus Brucella were recovered from 2 of 219 stools examined. The first positive specimen was obtained from a woman aged 54, who gave a history of ingesting raw goats' milk over a period of years in her youth. Her serum had an anti-abortus agglutinin titer of 1 to 60. This patient was afebrile at the time the specimen was obtained and had neither signs nor symptoms suggestive of brucellosis.

The second stool was secured from a patient about whom no data were available, except that she did not have clinical undulant

fever at the time the stool was obtained. Unfortunately, the patient is no longer under observation.

**Discussion.** This study of stools obtained from 219 patients indicates that individuals without febrile illnesses, without clinical suspicion of undulant fever, and without a history of the disease, may discharge Br. abortus from the intestinal tract.

Seventy-two of the 219 stools examined were obtained from patients who showed either abortus agglutinins in their sera, or a positive cutaneous reaction. Of the 38 patients with positive agglutinations, 17 had "reasonably adequate histories" of exposure to abortus infection. Twenty-four of the 34 patients with positive skin tests had similar histories. By "a history of adequate exposure" is meant either the ingestion of raw cows' or goats' milk for prolonged periods, or contact with cattle, goats or swine.

The viability of Br. abortus in a normal human stool, stored in a fruit jar at 8° C. for over 4 months, is of considerable interest.

**Summary.** 1. Brucella abortus was recovered from 2 of 219 stools obtained from patients who were not suspected clinically of having undulant fever.

2. Guinea pig inoculation of the stool sediments was substituted for the plate culture method of Amoss and Poston.

3. Brucella abortus, when mixed with human feces and stored at 8° C., remained viable for at least 150 days.

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# BOOK REVIEWS AND NOTICES

THE MICROSCOPIC ANATOMY OF VERTEBRATES. By GEORGE G. SCOTT, PH.D., Professor of Biology in the City College, New York City, and JAMES I. KENDALL, PH.D., Instructor in Biology in the City College, New York City. Pp. 306; 167 illustrations. Philadelphia: Lea & Febiger, 1935. Price, $3.75.

MOST textbooks of microscopic anatomy and histology deal chiefly with human material; they are written to meet the requirements of the student of medicine. The authors of this book present a survey of the microscopic anatomy of vertebrates in general. The text is concise, clearly written and illustrated by a number of very useful diagrams and photomicrographs. Selected references to recent literature are appended to each chapter. This is a good book for the college student who is taking a pre-medical course or a course in general biology; the more advanced student will find discussed a variety of subjects not usually included in the shorter texts on biology.

B. L.

OBSTETRICAL PRACTICE. By ALFRED C. BECK, M.D., Professor of Obstetrics and Gynecology, Long Island College of Medicine; Obstetrician and Gynecologist-in-Chief, Long Island College Hospital, Brooklyn. Pp. 702; 1053 illustrations. Baltimore: The Williams & Wilkins Company, 1935. Price, $7.00.

THIS new book on "Obstetrical Practice" gives, in a refreshingly simple manner and with a decided personal tone, the basic principles of obstetrics as taught in the Long Island Medical College. The conciseness of text, and the directness of treatment suggested, has much of benefit for the student or general practitioner, who needs guidance in obstetrical thought and therapy. For those who wish to read further there is appended to each chapter an excellent bibliography.

Of especial value are the discussions of Factors in Labor, the Mechanism of Labor and the Clinical Course of Labor. A conservative treatment of eclampsia is recommended; the author's mortality under this therapy is 6.5%. Throughout the book important points have been emphasized in heavy type, and nowhere to greater advantage for the practitioner than in the chapter on posterior presentations of the occiput. The author considers Braxton Hicks' version the best general treatment for placenta previa but gives his reasons for individualizing treatment by other methods.

Contracted pelves are considered under a modification of the classification of Caldwell and Moloy. The profuse use of line drawings in the enormous number of illustrations in the book serves to good advantage in the discussion of operative obstetrics. Here there are given definite indications and requisites for each operation. The advantage of the low-flap section is emphasized.

On the whole this new book is an excellent exposition of the views and teachings of a writer well qualified to express his individual opinions. The well-written straight forward discussions will make it of value to both students and practitioners.

P. W.

THE MEDICINE-MAN OF THE AMERICAN INDIAN AND HIS CULTURAL BACKGROUND. By WILLIAM THOMAS CORLETT, M.D., L.R.C.P. (LOND.), Professor Emeritus of Dermatology-Syphilology, Western Reserve University; Fellow of the Royal Society of Medicine of Great Britain, etc. Pp. 369; illustrated. Springfield, Ill.: Charles C Thomas, 1935. Price, $5.00.

ENTHUSIASTS of the aboriginal in the western hemisphere will find in this book, for all its informal and leisurely tone, all the absorbing interest its title promises. A generous and always judicious use of quotation from the literature of several centuries lends it many of the advantages of a well-edited anthology. But the author writes also out of a personal interest and experience that began early in his own career. The result is a book full of information imparted with a charm seldom found in such works. Save in the historic sense, it is, of course, not a strictly medical subject, since the medicine-man practised less medicine than shamanism, and ritual or trance were his treatment or his consultation. There are chapters On Indian Diseases, on Childbearing, and on Foods and Materia Medica, but the main body of the text treats *seriatim* the anthropologist's 15 culture areas of the Americas in the light of the practices and beliefs of their healers, who were, quite as much, also their priests. The author gives an engrossing account of the regional varieties of the healing art, that ritual through which the common tribespeople shared a little in the darker mysteries of their medicine-men. The book closes with a deeply felt lament for the passing of a great race and, with them, of things strange and dim that history may never be able to fix in its clear record.

H. B.

MAN, THE UNKNOWN. By ALEXIS CARREL. Pp. 346. New York: Harper & Bros., 1935. Price, $3.50.

FOR a general rather than any special audience, the author has undertaken to supply that heroic need, a synthesis of all that men know of themselves. Many of his already numerous readers will have considered that more than due regard is had also for what men have ground to hope for in one another: latent possibility is here treated as a coördinate of scientific truth; only the addition of potential to actual can yield even a rough estimate of the sum of all. Though in manner and method achieving all possible simplicity, it is yet a book whose enormous variety and compression of content is unlikely to satisfy either the too ignorant on many counts, or the very learned (certainly not the very opinionate) on any one. There are passages assured of offensiveness to the "orthodox" in politics, religion, science. Some readers may even be inclined to lay the book aside on the quite incidental provocation of its syntax—prevailingly declarative, even to the point of apparent dogmatism when the reader is in disagreement. According to the author's own apologia, however, almost every sentence, because of the vastness of the subject, must summarize the achievements of at least one man's whole lifetime of research; hence the book's effect of unremitting assertion.

The ordering of this immense complex of data has that fine clarity which comes as no surprise in a writer of the author's nationality. Not the handling, but the selection, the admission, of data, and the critical judgments passed upon them, are what here and there give pause. Probably but few of the author's confrères in science will have anything short of high praise for the central section of the book—its chapters summarizing present doctrine in the sciences of the body and those of the mind, its other chapters treating of Inward Time in its aspects physiologic and psychologic, of Adaptive Functions (their necessity for the development of personality,

their general neglect and actual atrophy in our civilizations). But there are frequent passages in which the author looks toward the future and prescribes for it, oft invoking the as yet unaccredited infant science of "metapsychics;" and in these his diagnosis of the human condition has more often the note of some prophet of old than of the contemporary clinician. Most of his readers will not be left with much doubt that the sickness charted is real, nor will many of them be at once agreed to submit to the drastic operation proposed. It will take much time and research to learn whether the author is wholly right about the mass of controversial matter upon which his own mind is decided even when it appears not to be consistent, yet the sum of knowledge and theory that he offers is so vast and broad and basic that the question of his being wrong in fundamentals scarcely arises, unless in the respect of their explicit application. Beset by these enigmas, each reader will decide for himself as he can, whether the author carries conviction when he tells us, in effect, that after the grand unsuspected discoveries of the past, will come other "impossibles," other unbelievables, which may—now, ages hence, or perhaps after all never, depending on our and our progeny's development of the human psychesoma's capacities—comprise the commonplace possessions of the race.

H. B.

MODERN OFFICE AND GENERAL PRACTICE. A Handbook of Practical Medicine. By DEANE R. BRENGLE, M.D. Pp. 320; illustrated. Kingsport, Tenn.: Southern Publishers, Inc., 1935. Price, $3.25.

AN encyclopedic arrangement of therapy in general practice.

The author anticipates the criticism of those whose opinions may differ from his by stating that he has put to clinical test each procedure recommended. However, the urologists, dermatologists and surgeons probably will not agree that certain of his suggestions should be followed by the general practitioner. The composition is more practical than scholarly. There are three interesting sections dealing with medical economics. The absence of any discussion of the anemias is a notable omission.

W. J.

IMMUNOLOGY. By NOBLE PIERCE SHERWOOD, PH.D., M.D., Professor of Bacteriology, University of Kansas, and Pathologist to the Lawrence Memorial Hospital, Lawrence, Kansas. Pp. 608; 27 illustrations, 8 colored plates and many tables. St. Louis: The C. V. Mosby Company, 1935. Price, $6.00.

THIS book should prove useful to medical students in conjunction with a regular laboratory course in immunity, as well as to graduates as a reference work, since it is largely made up of abstracts of the fundamental sources of immunologic knowledge to the date of publication. The book supplements textbooks of bacteriology, many of which are unnecessarily exhaustive studies for the second-year medical student.

The extreme detail concerning the technique of laboratory diagnosis of syphilis belongs in a manual of laboratory methods rather than in an introduction to the study of immunity. Sixty-seven pages on complement fixation seems too much in a book of this sort when such important work as that on influenza virus of Andrewes, Laidlaw and Smith, in England, and of Francis and Shope, in this country, is not mentioned specifically. There is also no mention, possibly because it is so recent a development, of the preservation of antisera in the dried "lyophil" form which is being used in the treatment of a variety of infectious diseases in several serum exchanges.

The book is very well printed and bound. The illustrations, diagrams and tables are clear and useful.

The author's style of writing is lucid, fluent and forceful. He has succeeded in presenting a difficult subject so clearly that the young student should be grateful to him for cutting away abundant underbrush.

H. P.

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BEITRAG ZUR KENNTNIS DES ILEUM TERMINALE FIXATUM UND ILEUS ILEI TERMINALIS FIXATI. By LENNART PETERSON. Eine anatomische, klinische und klinischstatistische Studie. (Vol. 75, Suppl. 32 of Acta Chirurgica Scandinavica.) Pp. 113; illustrated. Helsingfors: Mercators Tryckeri Aktiebolag, 1934. (No price given.)

IN the first portion of this monograph Peterson has classified abnormalities of attachment of the terminal ileum and emphasized that one or more of them occur in over 16% of individuals. The most common abnormality is a low attachment of the mesentery of the terminal ileum. Rarer but more familiar types are the Lane kink and Jackson's membrane (when the latter is attached to the ileum).

The fact that these anatomic variants have received so little attention in the past would seem to be explained by the author's statement that most of the cases are asymptomatic and cannot be diagnosed without abdominal section. There appears to be no relation between Ileum Terminale Fixatum and the incidence of appendicitis.

Its chief importance lies in the occurrence of ileus as a complication. Ileus Ilei Terminalis Fixati may arise by several different mechanisms such as kinking and volvulus. These are considered in detail in the second portion of the monograph. A study of reports from all parts of the world suggests that the particular form of ileus that occurs, is partly determined by the patients racial background, volvulus being more common in the East European peoples than in the West European and North American groups.

Although the author's experience indicates an incidence of ileus in 1.1% of cases of Ileum Terminale Fixatum, he was able to find only 120 clearly described cases in the literature. In his analysis of 2 series from Finland (185 cases, 1915–1930, and 31 cases, 1931–1932), the mortality was reduced from 59.5% to 45.2% in the second series.

The monograph is exceedingly thorough and should lead to a more fundamental understanding of a number of cases of acute intestinal obstruction occurring in the right lower quadrant. An English summary affords a terse if not very idiomatic introduction to the subject. I. R.

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A HISTORY OF SCIENCE, TECHNOLOGY, AND PHILOSOPHY IN THE 16th AND 17th CENTURIES. By A. WOLF, Professor and Senator, University of London; Head of the Department of History and Methods of Science, etc., with the coöperation of Dr. F. DANNEMANN, Professor in the University of Bonn, and MR. A. ARMITAGE, of University College, London. Pp. 692; 316 illustrations. New York: The Macmillan Company, 1935. Price, $7.00.

WHILE there may be much difference of opinion as to when the Middle Ages were finished, there is no doubt but that the 16th and 17th centuries witnessed the birth and marvelous growth of modern lines of thought and scientific discovery. It is fortunate for the reading world that the requirements of students pursuing courses in the history, methods and principles of science in the University of London have led the possessor of such encyclopedic knowledge and lucid style to give this detailed and well-

documented account. We subscribe to the author's "belief that the world has need of a new intellectual reorientation, and that to this end a close study of the history of human thought in its most objective spheres would be the best beginning." In addition to Astronomy, Mathematics, Physics Chemistry, Meteorology, Geology, and the biologic sciences, the author has included Geography, four chapters on Technology, Psychology, the Social Sciences and Philosophy. Such wide scope means that even in a book of these generous dimensions many subjects must be treated illustratively—as one soon learns on perusing one's own field—but the selections are well made and a happy medium struck between the occasional detail needed for a readable story and the masses of facts "required for" a reasonably full account. The abundance of carefully selected and for the most part well-reproduced illustrations adds further to the interest and value of this notable volume. It is to be hoped that the contemplated volumes on the 18th and 19th centuries and on the ancient and mediæval periods will be equally instructive and entertaining. E. K.

LOCALIZED RAREFYING CONDITIONS OF BONE. As Exemplified by Legge-Perthes' Disease, Osgood-Schlatter's Disease, Kümmell's Disease and Related Conditions. By E. S. J. KING, M.D., D.Sc., M.S. (MELB.), F.R.C.S. (ENG.), F.R.A.C.S., Honorary Surgeon to Out-Patients, Melbourne Hospital; Stewart Lecturer in Pathology, University of Melbourne. Pp. 400; 70 illustrations. Baltimore: William Wood & Co., 1935. Price, $7.50.

THIS well-written and elaborately documented monograph is comprised of "the greater part of the material which was submitted for the Jacksonian Prize of the Royal College of Surgeons in 1933." It is divided into four Sections:

Section I considers the formation of bone; its structure, composition, development and physiology. The pathology of bone rarefaction and abnormal calcification, together with the interpretation of the roentgenography of these processes, is also dealt with.

Section II deals with those localized rarefying changes in bone known as the osteochondritides. These changes are considered from their anatomic localization. This section comprises 197 pages and is the largest of the monograph.

Section III deals with posttraumatic rarefaction, both localized and diffuse.

Section IV chiefly considers rarefaction of the articular surface when associated with loose bodies in the contiguous joint.

The value of this book lies in that the author has brought together under a common heading a large number of heretofore isolated bone lesions. These lesions had cluttered the literature and confused the student through their designation by the name of the author first describing them. Some of the lesions reflected the nationalism of medical science by being weighted with the names of more than one "first describer," as in the case of Legge-Calvé-Perthes-Waldenström's disease of the proximal epiphysis of the femur.

That these epiphysial rarefactions were not a number of isolated diseases but constituted a single pathologic process occurring in different localities has been long known. The Reviewer has so dealt with them in his lectures during the past 6 years.

Little new has been developed by the author relative to the osseous lesions discussed. His work has been mainly one of erudite scholarship as con-

sidered from the standpoint of bibliographic research. This work he has performed splendidly though not, as he states, exhaustively.

To the great majority of clinicians and to many pathologists the author's monograph will bring clarity in a formerly confused section of bone pathology. For some time to come this monograph will be the definitive work on the osteochondritides. G. W.

JOHN WHITRIDGE WILLIAMS. Academic Aspects and Bibliography. By J. MORRIS SLEMONS. Pp. 109; 1 illustration. Baltimore: The Johns Hopkins Press, 1935. Price, $1.50.

THE author has performed a useful service in publishing in book form this presidental address before the Pacific Coast Society of Obstetrics and Gynecology. With the bibliography, Williams' contribution, it is now possible for many who never knew Williams in the flesh to become acquainted with the man who perhaps contributed more than any one else to scientific obstetrics during the past 30 years. Slemons has written here as an ardent student rather than as an experienced biographer; but still has done much to acquaint the world with the greatness of a very fine man. One must be impressed by the keenness of Williams' mind, as indicated by the range of his writing and by his energy when one sees a bibliography of 137 papers, not including his other more unofficial contributions.

A desirable addition would be more detail about Williams as the man rather than as the scientist. The human side is always more interesting than the intellectual to the average reader. It is hoped that the author may be persuaded to write a more extended biography sometime in the future. D. M.

## NEW BOOKS.

*Atlas of Pathological Anatomy, Vol. 2.* Issued under the Direction of the Editorial Committee of the British Journal of Surgery. Compiled by E. K. MARTIN, M.S., F.R.C.S. Pp. 475; 268 illustrations (168 in colors). Baltimore: William Wood & Co., 1935. Price, $15.00.

*Die Liquordiagnostik in Klinik und Praxis.* By DR. HANS HEMME, Privatdozent für Neurologie, Chefarzt der neurologischen Abteilung des Allgemeinen Krankenhauses Barmbeck in Hamburg. Pp. 205; 96 illustrations. München: J. F. Lehmanns, 1935. Price, Mk. 7.

*International Clinics, Volume 1. Forty-sixth Series, March, 1936.* Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 14 Collaborators. Pp. 314; illustrated. Philadelphia: J. B. Lippincott Company, 1936.

This 46th Series begins with an unusually eminent list of authors and a great predominance of medical subjects. Of especial interest to the Reviewer were the opening comprehensive article on Simmonds' Disease, suggestive papers on secondary and pernicious anemia, and the medical progress review of phosphatase activity and calcium and electrolyte metabolism.

*Endocrine Tumours and Other Essays.* By FREDERICK PARKES WEBER, M.A., M.D., F.R.C.P., F.S.A., Senior Physician to the German Hospital, London. Pp. 207. London: H. K. Lewis & Co., Ltd., 1936. Price, 7s. 6d.

*The Phenomena of Life.* A Radio-Electric Interpretation. By GEORGE CRILE. Edited by AMY ROWLAND. Pp. 379; 113 illustrations and 22 tables. New York: W. W. Norton & Co., Inc., 1936. Price, $3.50.

*Twentieth Century Psychiatry.* Its Contribution to Man's Knowledge of Himself. By WILLIAM A. WHITE, M.D., A.M., SC.D. Pp. 198. New York: W. W. Norton & Co., Inc., 1936. Price, $2.00.

*Foundations of Short Wave Therapy.* Physics—Technics—Indications. Physics and Technics by WOLFANG HOLZER, DR. MED., Assistant in the Physiological Institute of the University of Vienna. Medical Applications by EUGEN WEISSENBERG, DR.MED., Medical Superintendent of the Short Wave Section of the University Clinic for Nervous and Mental Diseases in Vienna. Translated by JUSTINA WILSON, F.R.C.P. (EDIN.), D.M.R.E. (CANTAB.), and CHARLES M. DOWSE, B.SC. ENG. (LOND.), A.M.I.E.E. Pp. 228; 53 illustrations and 10 tables. London: Hutchinson & Co., Ltd., 1936. Price, 12/6.

*Insulin.* Its Production, Purification and Physiological Action. By DOUGLAS W. HILL, B.SC. (BRIS.), PH.D. (LIV.), Lecturer in Chemistry, University College, Exeter; Special Lecturer in Organic Chemistry, University of Bristol, and FREDERICK O. HOWITT, M.SC., PH.D. (LOND.), F.I.C. Foreword by PROFESSOR E. C. DODDS. Pp. 219; 6 photomicrographs and 7 tables. London: Hutchinson & Co., Ltd., 1936. Price, 12/6.

*The Specificity of Serological Reactions.* By KARL LANDSTEINER, M.D., The Rockefeller Institute for Medical Research, New York City. Pp. 178. Springfield, Ill. Charles C Thomas, 1936. Price, $4.00.

*Seuchenentstehung und Klimaforschung.* Die Ergebnisse der Klimaforschung in Ihrer Bedeutung für die Epidemiologie. By DR. MED. FRIEDRICH WOLTER, Leiter des Hamburgischen Forschungsinstituts für Epidemiologie. Pp. 43; 9 tables. Stuttgart: Hippokrates-Verlag G.m.b.H., 1936. Price, RM. 3.75.

The author tries to show that epidemic diseases are miasmatic in nature, and that they are caused by changes of the soil and of the climate.

*Die Entstehungsursachen der Haffkrankheit.* In dem Zeitraum von 1924–1933 vom epidemiologischen Standpunkt. By DR. MED. FRIEDRICH WOLTER, Leiter des Hamburgischen Forschungsinstituts für Epidemiologie. Pp. 56; 2 tables. Stuttgart: Hippokrates-Verlag G.m.b.H., 1936. Price, RM. 4.50.

This is an attempt to show that the "Haffkrankheit" is a rare type of the epidemic disease, the miasma causing it being a gas formed in the water of the bay polluted by the waste waters of Königsberg.

*Les Parathyroides.* First Fascicle, Volume 2, of Traité d'Endocrinologie. By C. I. PARHON, Professeur à l'Université de Jassy, and M. GOLDSTEIN, Docent à l'Université de Bucarest. Pp. 524; illustrated. Jassy: H. Goldner, 1935. Price, francs 40.

## NEW EDITIONS.

*An Index of Differential Diagnosis of Main Symptoms.* By various writers. Edited by HERBERT FRENCH, C.V.O., C.B.E., M.A., M.D. (OXON.), F.R.C.P. (LOND.), Consulting Physician to Guy's Hospital; late Physician to H. M. Household. Pp. 1145; 742 illustrations, of which 196 are colored. Fifth Edition. Baltimore: William Wood & Co., 1936. Price, $16.00.

*A Guide to Psychiatric Nursing.* By F. A. CARMICHAEL, M.D., Superintendent, Osawatomie Hospital, Osawatomie, Kansas; Lecturer in Clinical Psychiatry, University of Kansas Medical School, Kansas City, and JOHN CHAPMAN, M.A., M.D., Sometime Associate in Psychiatry, Osawatomie State Hospital, Osawatomie, Kansas. Pp. 175; 31 illustrations. Philadelphia: Lea & Febiger, 1936. Price, $2.25.

*Dental Infection and Systemic Disease.* By RUSSELL L. HADEN, M.A., M.D., Chief of the Medical Division, Cleveland Clinic, etc. With a Foreword by DR. EDWARD C. ROSENOW. Pp. 163; 63 illustrations. Philadelphia: Lea & Febiger, 1936. Price, $2.50.

# PROGRESS
OF
# MEDICAL SCIENCE

## THERAPEUTICS

UNDER THE CHARGE OF

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### THROMBOPENIC PURPURA AND SOME OTHER HEMORRHAGIC DISEASES.

In the past few years there has been renewed interest in hemorrhagic diseases, which has resulted in a change of concepts regarding their etiology and treatment. There has also resulted a rather indiscriminate use of hemostatic agents, which has served to confound rather than to clarify understanding. In many reports data are inadequate and poorly controlled. Consequently one is forced to accept new remedies with cautious conservatism.

**I. Thrombopenic Purpura.**—The etiology of thrombopenic purpura is unknown. Older theories ascribing the disease to bone-marrow disturbance, either as a primary dyscrasia or as a reaction secondary to injury[1] have not been confirmed by subsequent study. There are also valid objections to the theory of splenic malfunction,[2] even though splenectomy provides striking benefit in most cases. Indeed, it is questionable whether platelets play an essential part in the causation or mechanism of thrombopenic purpura. Studies by Bedson[3] and Roskam[4] with platelet antiserum indicate a dual mechanism responsible for experimental purpura, dependent on thrombopenia and altered vascular reactivity. It is apparent, however, that clinical purpura occurs also without platelet changes, as in "anaphylactoid" purpura and scurvy, where the vascular component alone appears to be involved. Recent studies by Gratia and Linz[5] on the Shwartzman phenomenon suggest that the difference between local erythema with purpura and generalized purpura with thrombopenia and anaphylactic shock is quantitative rather than qualitative. Therefore, it is possible that thrombopenia, when it occurs, is simply another manifestation along with altered vascular reactivity of the same underlying state, and that the distinction between thrombopenic and non-thrombopenic purpura

is unwarranted. "The connection between capillary damage and thrombopenia may be reciprocal and the symptoms may follow a common insult."[6]

Current opinion, thus, suggests an allergic state as the cause of thrombopenic purpura. Although earlier observations by Osler,[7] Meleney,[8] and Alexander[9] indicated clearly such a mechanism in "anaphylactoid" purpura, it is only recently that thrombopenic purpura also has been included in this group. The present point of view has been supported by observations on known agents as arsphenamin, quinin, "sedormid," "nirvanol," milk and other foods, and possibly bacteria sensitivity to which has provoked thrombopenic purpura indistinguishable from "essential" thrombopenia. McCarthy and Wilson[10] reported 2 cases and reviewed 79 recorded in the literature of blood dyscrasias following arsphenamin injection. In one group of 12 cases, thrombopenic purpura alone developed without red cell or white cell disturbance. "All the cases of this group developed only after considerable treatment with numbers of injections, and it is probable that a specific sensitivity towards the arsphenamins gradually took place." Rich[11] described a similar case with thrombopenic purpura occurring abruptly after the sixteenth injection of neoarsphenamin, likewise with prompt recovery on withholding further arsphenamin injection. He attributed the reaction to a "destructive action" in the peripheral blood stream. Loewy[12] reported 3 cases of thrombopenic purpura following the prolonged administration of the hypnotic "sedormid." The drug had been taken in the usual therapeutic doses without harm. However, the patients acquired a sensitivity to the drug, described by the author as an "allergo-toxic" effect. Peshkin and Miller[13] observed a woman with thrombopenic purpura, which recurred four times under observation after administration of either quinin or ergot, although in childhood "quinin had been liberally administered with apparent tolerance." Jones and Jacobs[14] reported a case of thrombopenic purpura in a girl 9 days after onset of "nirvanol" therapy for chorea. Landsberger's[15] case of thrombopenic purpura was demonstrated to be due to sensitivity to cow's milk. Brinnitzer[16] reported a similar reaction in a child with thrombopenic purpura brought on twice following transfusion with compatible blood from the patient's mother. Squier and Madison[17] have demonstrated that specific sensitization to certain foods may be the cause of thrombopenic purpura in some cases. McLean and his coworkers[18] have observed 11 cases of thrombopenic purpura occurring 6 to 21 days after the subsidence of acute infection, "which suggests the possibility, clinically at least, that thrombocytopenia may be an allergic manifestation."

Thus it is implied that essential thrombopenic purpura may be a similar reaction to those enumerated but provoked by agents as yet unrecognized. Whether or not this concept is correct, it has served as a working hypothesis for the newer therapeutic measures. The aim, therefore, has been directed at two factors: 1, removal of the exciting agent, such as drugs; 2, alteration of the fundamental allergy or hypersensitive state. The second approach may be involved in the beneficial effects reported on the use of snake venom.

*Snake Venom Therapy.* Stockton and Franklin,[19] in 1931, reported the arrest of hemorrhage after injection of antivenin in a case of acute thrombopenic purpura, which had failed to respond to other therapy. Bothrops antivenin, a serum globulin obtained from blood of horses immunized against Bothrops venom was used. Because of previous horse serum therapy, the patient was desensitized first with two intracutaneous injections of 0.1 and 0.2 cc. respectively at half-hour intervals and then given 10 cc. of the antivenin subcutaneously. Bleeding stopped in 24 hours.

Taylor,[20] in 1933, reviewed 7 cases of thrombopenic purpura previously reported, as well as his own, treated by either crotalic or bothropic antivenin. There were 2 deaths and 5 recoveries. His method of administration was not stated precisely. Presumably 10 cc. of bothropic antivenin may be given intramuscularly, and this may be followed if necessary, by doses of 5 to 10 cc. for several days. "Provided sensitization to horse serum is not extreme, a trial of bothropic antivenin should, in the writer's opinion, be made in all cases before splenectomy is undertaken. In fulminating cases, it may be given intravenously, the usual precautions against protein shock being observed, in a dosage of 10 cc., repeated several times in 24 hours, if necessary, or at daily intervals." The data are insufficient as yet to judge the efficacy of this therapy. Its benefit is said to be derived from anti-hemorrhagins and anti-hemolysins.

Recently Peck and Rosenthal[21] reported an impressive series of cases of bleeding disorders treated with moccasin snake venom. Peck had observed, in 1931, that when this venom was injected into a rabbit, it rendered the animal refractory to a subsequent Shwartzman reaction. Because of the analogy of this reaction to clinical purpura, the subcutaneous injection of moccasin venom was tried in cases of purpura and in other diseases characterized by an abnormal bleeding tendency. Definite benefit was claimed in "anaphylactic" and "toxic" purpura, in several cases of thrombopenic purpura, as well as in the bleeding of multiple telangiectases, bronchiectasis, functional uterine bleeding, etc. The effect was ascribed to a change in the vessel walls. The mode of administration was as follows: moccasin venom was prepared in ampoule form as 1 to 3000 solution. The initial dose was 0.4 cc., injected subcutaneously in the arm or thigh. The amount was then rapidly increased to 0.8 or 1.0 cc. as a maximum dose, which usually was given twice weekly for 3 months. The patient's maintenance dosage was then determined according to the hemorrhagic symptoms. For children, the corresponding initial dose was 0.2 cc. and the maximum dose 0.6 cc. Many patients developed a local reaction of hypersensitivity to the venom after the fourth or fifth injection. In most cases this was overcome by reducing the following dose to 0.05 cc. of 1 to 3000 dilution, and at each subsequent injection increasing the amount until reaching the required dosage. Rarely greater dilution and more cautious desensitization was needed. This form of therapy needs further confirmation before it may be considered acceptable.

The venom of certain snakes is characterized by clot-accelerating ability on the formed elements of the blood. These venoms have been used locally to arrest accessible bleeding occurring in purpura, hemo-

philia and other bleeding conditions. MacFarlane and Barnett[22] have reported success with the Russell viper in 1 to 10,000 dilution, and Rosenfeld and Lenke,[23] with tiger snake venom in 1 to 5000 dilution. Activity was attributed to a thrombin-like substance.

*Dietary Measures.* In current articles on the treatment of purpura, stress is laid on the need of high vitamin, high protein diet, as well as of iron to help recovery from anemia of blood loss. Kugelmass[24] claimed benefit with a diet rich in protein and fat. However, there is little experimental or clinical evidence to justify this point of view. When the patient is undernourished such a régime is warranted, but purpura, in our experience, shows no predilection for undernourished persons, nor does the dietary of patients with purpura reveal itself characteristically low in vitamin or protein-containing foods.

Following the isolation of hexuronic acid from citrous fruits and from adrenal cortex by Szent-Györgi, in 1928.[25] there has developed widespread interest in the relationship between vitamin C metabolism and hemorrhagic disease. Apparently latent scurvy can be precipitated not only by insufficient intake of the vitamin but also by changes in the intermediary metabolism in the course of chronic infections[26,27,28] and probably by interference with absorption, as in disease of the gastro-intestinal tract. It may be that certain cases of "purpura" occurring under such conditions are in effect scurvy, and that vitamin C therapy would be beneficial. Because of its relationship to the integrity of bloodvessels, vitamin C has been administered also in other bleeding disorders. Vogt[29] reported the arrest of uterine hemorrhage in 4 young women, 1 of whom had thrombopenic purpura, by the intravenous injection of cevitamic acid. Junghans[30] claimed to have arrested hemorrhage in 33 of 35 patients with severe menorrhagia, mostly of the premenopausal type, with 100 mg. of cevitamic acid injected daily intravenously. Bleeding stopped in 4 to 6 days. Böger and Schröder[31] reported that they had checked bleeding in every class of hemorrhagic diathesis, including thrombopenic purpura, by the intravenous injection of 100 to 300 mg. of cevitamic acid daily. These claims appear extravagant to us. In our hands, at least, this therapy has been of no value in the treatment of thrombopenic purpura.

*Transfusion.* In a certain number of cases spontaneous recovery occurs. Because of this a conservative[18,32] attitude towards purpura has been advocated. Large direct or whole blood transfusions[33] have been advised. Jones and Tocantins[32] observed that daily transfusions of 200 to 300 cc. are usually more beneficial than isolated large transfusions in checking the hemorrhage of purpura. This also has been our experience. Citrated blood apparently is as effective as direct, or whole blood transfusion.

*Roentgen Ray.* Roentgen ray therapy directed over the spleen has been advocated for many years.[34] Recent reports by Hippe and Kochmann[35] and others record gratifying results. Other reports are less favorable. The differences may be due to the selection of cases and to the varying modes of administration. In our experience, this form of therapy has been disappointing.

*Splenectomy.* Eliason and Ferguson,[36] reviewing 213 cases in the literature up to 1932, found that 88% of patients with chronic thrombopenic purpura and 65% of those with the acute forms were cured by splenectomy. The operative mortality of the entire group was 13%, whereas in the last 4 years the operative mortality had been 7% in 113 cases. The higher figure was attributed to the poor operative risk of the earlier group of patients. The authors emphasized the need of preparation by transfusion in these patients. There still remains controversy over the optimal time for splenectomy. Conservative judgment suggests the advisability of waiting for temporary remission. However, "uncontrollable bleeding, whether sudden and severe or recurrent, appears to be the indication for splenectomy in purpura hemorrhagica."

**II. Bleeding Tendency in Obstructive Jaundice.**—The bleeding tendency in jaundice has been attributed to lack of available calcium, retention of bile constituents, decreased fibrin or fibrinogen, excess of heparin, etc., but later studies have not confirmed such hypotheses. The extensive literature on this subject is reviewed in articles by Wangensteen[37] and others[38–41]. Recently anoxemia,[39] and lack of prothrombin,[40] and excess of cystein[41] have been suggested as causes of the phenomenon. Since the mechanism is not clearly understood, the prediction of hemorrhage in jaundiced patients has been uncertain. Apparently as increased sedimentation rate, described by Linton,[42] is not a constant feature in these cases.[38,43] Certain authors [38,44] believe that the intensity and duration of jaundice and a prolongation of clotting time are a better index of the bleeding tendency. Quick[40] and others believe that it may be detected by a prolonged prothrombin time.

Notwithstanding theoretical objections to calcium therapy, there are still many who attest to its efficacy, either in the form of calcium chlorid, as proposed by Lee and Vincent[44] and Walters,[45] or in the form of the gluconate. Walters prepared patients with obstructive jaundice for operation by administering large amounts of glucose by mouth and by rectum, and also by injecting intravenously 5 cc. of a 10% calcium chlorid (prepared in redistilled water) daily for 3 days before operation. He believed that this prevented postoperative hemorrhage. However, probably the most reliable measure for preventing and combating hemorrhage in jaundice still appears to be transfusion. Judd[39] and his coworkers have pointed out that if surgery is indicated in jaundiced patients, it is advisable to force both enteral and parenteral glucose, and to give blood transfusions before and after the operation.

**III. Hemophilia.**—The mechanism underlying the prolonged clotting time and bleeding tendency in hemophilia is still unknown. Older theories attributed the abnormality to calcium deficiency,[46] to thrombokinase defect,[47] to excess of antithrombin,[48] and to prothrombin defect.[49] More recent work, however, suggested rather that the abnormality resided in a peculiar platelet stability resulting in a slow liberation of prothrombin (according to some) or thrombokinase (according to others) with consequent delay of clot formation.[50,50a] The defect, thus, has been laid to a qualitative change, and therapy accordingly has been aimed at acceleration of coagulation. Although accessible bleeding

apparently can be checked by local hemostatic agents,[22,23] attempts to alter the fundamental clotting defect have been unsuccessful. The beneficial effect of ovarian therapy, reported by Birch[51] has been disclaimed by other workers.[52] Until recently the most dependable method of shortening clotting time and checking bleeding has been transfusion of blood. In our experience, this usually can be done with small transfusions either of citrated blood or plasma.[53]

Recent studies by Eley[54] have been most promising for a specific therapeutic agent. Following the previous reports by Mills[55] that "tissue fibrinogen" prepared from bovine lung tissue shortened the clotting time and arrested the hemorrhagic phenomena in this disease, Eley prepared a tissue protein extract from human placenta which provided a more marked and lasting effect. With the oral administration of from 5 to 15 cc. of this material two to three times daily, the clotting time was reduced to normal limits for from 2 to 9 days. In 11 of 15 cases there was remarkable success. Older patients were apt to be refractory; in certain of these the intramuscular injection of 5 to 10 cc. of the material gave a satisfactory response. This material was also very effective in arresting accessible bleeding in other hemorrhagic conditions.

**IV. Miscellaneous Hemostatic Agents.**—In Europe, several new drugs have had recent vogue in the treatment of bleeding disorders. "Nateina," a proprietary which is said to be a mixture of vitamin concentrates and calcium phosphate, has been advocated for the treatment of hemophilia.[56] Reports have not been universally favorable.[57]

"Sangostop," a proprietary made of a solution of apple pectin, has been advocated for non-specific bleeding. It is marketed in 1.5% solution for parenteral use. Brahn and his coworkers[58] found that it shortened clotting time in rabbits. Sack[59] reported the prompt arrest of bleeding in 32 cases of hemorrhage after the injection subcutaneously or intragluteally of 20 to 80 cc. It was administered orally in 5% solution particularly for cases of gastric hemorrhage. In 3 patients with hemophilia there was also apparent benefit from this therapy.

Congo red in 1% aqueous solution has been administered with success in severe cases of thrombopenic purpura. Brühl[60] reported the prompt arrest of bleeding in 4 cases which had failed to respond to the usual measures. The dye was injected intravenously in doses of 10 to 20 cc. without causing untoward reactions. Bleeding stopped within 4 to 12 hours. Its mode of action was unexplained.

These agents may prove to be of distinct value. Unfortunately we have had no experience with them, and therefore an appraisal of their worth would be untimely.

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## RADIOLOGY

UNDER THE CHARGE OF
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**Lesions Involving the Lung and Pleura.**—The necessity of knowing the exact position and shape of a lesion is a fundamental requisite to the proper interpretation of the roentgenographic images of lesions involving the lung. Levitin and Brunn,[6] in a study of the roentgenologic appearance of the lobes of the lung and the interlobar fissures, have provided a series of excellent illustrations depicting the free portions of the individual lobes and the overlapping portions in their relation to one another. In a series of 32 drawings they exemplify the various shadows observed in different types of lesion. Sixty-four reproductions of roentgenograms compare the findings in films made in the postero-anterior projection with those observed in those made in the lateral projection.

Roentgenograms exhibit superimposed shadows of a three-dimension object projected on a flat plane. The shadows are of two dimensions and do not give a true picture of the shape of the process and its location. To bring out the third dimension, stereo-roentgenograms are often made. The use of postero-anterior and lateral projections afford two films in planes at right angles to each other, which is of great aid in studying the position and shape of the parts under consideration.

Processes occurring in the interlobar septa offer particular difficulty in interpretation on a single postero-anterior projection. Because of the oblique position of the septa, the horizontal ray projects the shadow of the septa on the roentgenogram as a broad surface, giving the impression of a diffuse area of lung involvement. Stereo-roentgenograms do not bring out the true nature or location of this process. A lateral view, in the same plane as the interlobar fissure, affords a totally different conception of the limits of the process.

The authors qualify their interpretations of the roentgenograms published with the statement that all disease processes affecting these divisions of the lung would not occupy the areas designated in their diagrams: previous disease of the lung may have resulted in retraction, distortion, or displacement of the lung under consideration. The entire interlobar septum usually is not involved by the disease. Likewise, only a portion of one or more lobes may be affected. The general configuration of the affected parts, however, closely simulates the diagrams experimentally produced.

They point out that lung abscesses are most frequent in the superior division of the right lower lobe, and primary carcinoma of the lung infrequently occurs here. Pneumonia of the lower lobe is more frequent in

the superior division of the right side, and because of its central appearance on the roentgenogram is often called "central pneumonia." The physical signs of the process are found in a small circumscribed area posteriorly between the scapula and spine and between the fourth and eighth ribs.

Atelectasis, especially postoperative, is frequently found in the inferior division of the right lower lobe. Physical signs of atelectasis of this portion of the lung are frequently absent despite considerable involvement as seen on the roentgenogram. If atelectasis is of long duration, there is considerable diminution in size of the involved lung. The superior division of the lower lobe will become emphysematous and fill the posterior recess behind the diaphragm. Normal breath sounds and resonance are found posteriorly. Likewise, anteriorly the clear middle lobe will mask the involved lung. Dullness, if elicited, is continuous with the liver dullness.

It is interesting to note the infrequency of involvement of the entire left upper lobe by pneumonic consolidation, and the infrequency of effusion in the interlobar fissure. The left lower lobe was found to be as frequently involved by pneumonia as the right lower lobe. It also showed similar division of involvement in the superior and the inferior portion.

Physical signs of involvement of the interlobar fissure between the right upper and right lower lobe may be absent, because this fissure approaches the chest wall only in the axilla—its narrowest part. In the interlobar fissure between the right upper and right middle lobe the process is overlapped by considerable lung which, if not involved, cannot transmit the dullness of the effusion. An interlobar fissure completely surrounds the right upper lobe, a combination of that between the right upper and right lower lobes and the fissure between the right upper and right middle lobes. Because of the broad shadow obtained in the postero-anterior projection, which is less dense centrally near the hilus, involvement of these two fissures has often been misinterpreted as lung involvement and frequently as lung abscess. It is the posterior fissure, lying obliquely, which accounts for the broad shadow. The lateral projection clearly demonstrates the contour of this fissure.

Effusion between the middle and lower lobes is the most frequent of all interlobar effusions. The oblique course of this fissure explains the broad shadow seen in the roentgenogram in the postero-anterior projection.

Atelectatic lung is smaller than the normal lung. The middle lobe is a small lobe and when atelectatic may diminish so in size as to approach the dimensions of a large effusion between the lobes.

A high diaphragm superimposed over the cardiac shadow is frequently confused with an interlobar effusion between the middle and lower lobes. A superimposed pendulous breast may cast a shadow which can be erroneously interpreted as an interlobar effusion. The right interlobar fissure bordering the upper surface of the lower lobe is the major fissure separating the lobes. This fissure separates the lower lobe from the upper posteriorly (from the hilus to the posterior chest wall) and the lower lobe from the middle lobe anteriorly (from the hilus to the anterior chest wall). Effusion in this area can easily be mistaken

for a large tumor. A roentgenogram in the lateral projection clearly establishes the position of the shadow within the interlobar fissure. Interlobar effusions involving the fissure between the left upper and the left lower lobes are not common. Exudates in the interlobar fissures are by no means as infrequent as the paucity of reports in the literature would indicate. Stivelman[11] asserted that they cast shadows which are frequently misinterpreted. They may occur in any of the fissures; in one instance an exudate was found in the azygos fissure. In his experience, they account for many of the so-called mild and atypical pneumonic processes, and occasionally are confounded with intrathoracic neoplasms. Many cases of unresolved pneumonia, when not due to tuberculous processes, are either primary interlobar exudates or exudates complicating recently resolved pneumonic infections. Transudates secondary to circulatory failure may accumulate in interlobar fissures and closely simulate pulmonary consolidation or intrathoracic neoplasm. Clinically, an interlobar exudate may develop with so few constitutional disturbances and such moderate pain and cough that its accidental discovery on the roentgenogram may be disconcerting. As a rule, it makes its appearance in much less stormy fashion than lobar pneumonia, and while at times the cough may be quite distressing there is no bloody sputum. The paucity of physical findings in interlobar pleurisy is in itself of diagnostic importance. A critical drop in temperature is rarely observed in interlobar exudate, nor does the blood count show as high a leukocytic response and preponderance of neutrophils as it does in pneumonia. Interlobar exudates will rarely simulate endobronchial neoplasms with atelectasis of the tributary lung area, displacement of the trachea and mediastinal contents toward the involved side, narrowing of the interspaces and retraction of the diaphragm on the side of the lesion. In carcinoma with alveolar involvement, and in those casting a shadow in the hilum that extends toward the periphery, confusion with interlobar collections of fluid may occur. If roentgenograms in the lateral projection show these shadows to be intimately connected with an interlobar fissure, time and patience may be necessary to demonstrate the gradual disappearance of the shadow that will substantiate the interpretation of an interlobar exudate. The necessity of the postero-anterior and true lateral projection in the making of roentgenograms for studying of this type of lesion is stressed.

Baum[1] believed that electrosurgical severance of pleural adhesions may convert an ineffective artificial pneumothorax into an effective one. Since thoracoscopy is relatively harmless, intrapleural closed pneumolysis should be the treatment of choice in ineffective artificial pneumothorax. When adhesions become organized, forming fibrous strings, cords, bands, or fans, which prevent the tuberculous cavity from collapsing, or which, by contraction, cause a reëxpansion of the collapsed lung and reopening of the cavity, the aid of the roentgenologist may be invaluable. In questionable cases, the roentgenologist should not commit himself, because the roentgenographic picture differs frequently from the thoracoscopic. The final decision as to the procedure of intrapleural closed surgery should never be made on roentgenologic evidence alone.

In an effort to visualize intrapleural adhesions to decide which were

the chief factors in preventing proper collapse, or in holding open a cavity, Ellison[4] used oblique plane exposures of the hemothorax in which the pneumothorax existed. By using a lead screen covering half of the cassette (14″ by 17″) in the long diameter and changing the screen position between exposures, he juxtaposed one view made in an anterior oblique plane and one made in a posterior oblique plane on one film. This, with one roentgenogram made in the postero-anterior plane, gave him more information than he had in one set of roentgenograms made stereoscopically. The angle of rotation used to obtain the oblique views was about 45° from the plane of the film. In making the exposure in the posterior oblique position the forearm on the involved side was placed across the small of the back and in the anterior oblique position the arm was rotated inwards and the point of the shoulder was brought forward as far as possible. All exposures were made during the expiratory phase of respiration.

Encountering difficulty in the administration of gas to a patient in whom formerly there had been no difficulty, and whose fluoroscopic tracing showed a well collapsed lung, suggested to Blady and Cohen[2] the possibility of giving the treatment under fluoroscopic guidance. This was accomplished without difficulty with the aid of the fluoroscope. Since that time a weekly clinic at which difficult cases were treated under fluoroscopic guidance has proved of inestimable value and has produced gratifying results. The usual method is to observe the patient in the upright position, turning him until the suitable angle for the individual patient is determined. A direct tracing of the chest and the relative positions of the heart, trachea, hilar regions, diaphragm, and position and shape of the collapsed lung is made. The patient then lies down on the unaffected side and the affected side is fluoroscoped, using the horizontal ray. The findings are traced on a 14″ by 17″ celluloid transparency. From study of the two tracings the most suitable point for insertion of the needle is located. The needle is introduced under fluoroscopic control. All guess work in the difficult cases has been replaced by direct observation and accurate guidance.

Generalized pleural effusion accompanying congestive heart failure is observed frequently, but localized effusion with heart disease has not been emphasized. Shiflett[10] found records of localized interlobar effusions increasing as symptoms became severe and decreasing coincident with clinical improvement.

It is generally agreed by internists and pathologists that the lungs of the adult are relatively immune to syphilitic infection. There is ample pathologic evidence of the luetic etiology of the massive interstitial consolidation or white pneumonia of infants. Robinson[9] found reports of 12 cases from 2,800 autopsies at Johns Hopkins Hospital. Only 4 of these were in adults; 3 of the 12 had been recognized clinically. In 20,000 patients admitted to the Munster Clinic, Krause had observed only 5 cases. Roentgenologically, he found three types of lesions described: 1, Generalized thickening of all the bronchial markings, studded with minute "knobby" enlargements, radiating from the hilus into one or both lung fields and producing a characteristic fan-shaped effect, a diffuse interstitial fibrosis of the bronchial tree. Assmann described this lesion which, if bilateral, may be confused with the infil-

trative type of metastatic malignancy. If unilateral, it may simulate primary bronchogenic carcinoma of the infiltrating type. 2, Gumma of the lungs, which may be miliary and multiple or solitary, discrete masses several centimeters in diameter, appearing as nodular areas of increased density, usually near the hilus, or in the periphery of the lung field. In the early stages of development of these nodular areas a delimiting zone of pneumonitis is formed about them, this is replaced later by a fibrous connective-tissue capsule. Necrosis may present as an area of rarefaction in the central portion of the nodule, or fibrosis may occur. In the early stage of the solitary discrete mass, especially if it is situated in the periphery of the lung, the condition may be confused with lobular tuberculosis or abscess formation. In the later stage of encapsulation, when located near the hilus, it may simulate a primary malignant tumor. The miliary form may be erroneously interpreted as metastatic malignancy. 3, The diffuse lobar form, which is occasionally described as a clinical entity, is really a massive atelectasis secondary to bronchostenosis due to syphilis of the primary bronchus. Ordinarily, in uncomplicated syphilis of the lung, cavitation only occurs in the terminal stages, and then as a result of bronchial dilatation and bronchiectasis. Calcification has never been noted in syphilis of the lung. There are no pathognomonic roentgenographic images of syphilis of the lung. Various observers have credited the lesion with a predilection for the middle lobe of the right lung, the hilar zone in one lung field, or the base of one lung. Symptoms and signs are quite variable, usually dependent on the nature and extent of the lesion; they may even be absent. They may be manifested by a dry, trivial cough or the expectoration of a mucopurulent sputum, with febrile reaction and all signs of an active tuberculosis. A sudden and severe hemoptysis may be the first symptom. In a case of syphilitic tuberculous symbiosis, with sputum showing positive findings of tubercle bacilli, an associated syphilis of the lung would never be suspected. Many cases are probably missed or confused with tuberculosis or tumor of the lung, which may account in part for the rarity of the disease. The case he reported was in a negress, aged 36, which conformed to all the criteria laid down for a diagnosis of syphilis of the lung, namely, syphilitic history, signs and symptoms of a chronic, stubborn, progressive pulmonary lesion, repeated examinations with failure to find tubercle bacilli in the sputum, positive serology and a lesion which roentgenographically was more extensive than the physical condition of the patient warranted. Response to specific therapy was prompt and lasting. Wigby and Sanders[13] reported a case of gumma of the lung in a negro, aged 34, with surrounding syphilitic pneumonia which was found at necropsy.

Fruchter,[5] in discussing discrete pulmonary lesions, presented a type of pulmonary tuberculosis to which Abbert, Fraenkel and Straub recently called attention occurring as isolated, sharply defined, coin-sized, round encapsulated shadows with no reaction in the surrounding tissues. These may develop with or without fever and with positive or negative findings in the sputum examinations. The foci may remain stationary for years, even in the presence of a progressive and finally fatal tuberculosis elsewhere. They may eventually progress, however, and go on to liquefaction and cavitation, extending into the surrounding

tissue by the formation of daughter foci. These lesions constitute a rare form of exudative focal tuberculous inflammation isolated by a connective tissue capsule. One has difficulty in differentiating these lesions from tumor metastases, which commonly appear as discrete pulmonary shadows. They may simulate non-tuberculous bronchopneumonia, syphiloma, cysticercosis, and echinococcus cysts. The clinical history has a prominent place in making the differential diagnosis. Repeated or serial roentgenograms to study the morphologic changes are all but indispensable.

Pulmonary calcifications interested Aristotle and since his time have fascinated the minds of generations of medical investigators. Pendergrass and de Lorimier[7] stated that the biogenetic nature of their development is not known. Wells, after an exhaustive study, concluded that there seemed to be no essential differences between the processes involved in normal ossification and in most instances that of pathologic calcification; any area of calcification may be changed to true bone in the course of time. In general, when one attempts to account for calcified lesions in the lungs, these four possibilities are to be considered: 1, Secondary calcification after degeneration or necrosis due to infection; 2, primary or secondary calcification of aspirated foreign bodies; 3, precipitation of the osseous inorganic elements, due to excessive concentration of these in the blood; and 4, metastases of bone-forming cells. Concretions of grossly visible dimensions, produced by any of these four general types of processes, are spoken of as "pneumoliths," "lung calculi" or "lung stones." When parenchymal concretions erode through the walls of the bronchi and become free in the lumina of the bronchi or bronchioles, the term "broncholith" is applied. These broncholiths are irritating to the mucosa, a cough reflex is stimulated and with cough a change in the position of the broncholith occurs with further irritation. Bronchorrhea (excessive secretion of mucus) and bronchial colic (bronchial spasm) with wheezing and expiratory dyspnea are the underlying causes of a symptomatology often described as "stone asthma." Paroxysmal cough is the rule, sometimes climaxed by an explosive effort which usually results in expelling a stone or gritty material. Pain, tearing or cutting, localized to the poststernal region or referred to one or the other lateral portion of the chest results from the cough paroxysms. Hemoptysis usually occurs with the passage of a stone; it may occur repeatedly during the coughing attacks, or occur periodically over several weeks or months. Many of these cases are considered to be pulmonary tuberculosis, notwithstanding repeated negative examinations of sputum. If secondary infections occur the condition becomes masked by the symptoms and signs of chronic bronchitis, bronchiectasis, abscess or pneumonia. Roentgenologic examination and recognition of the concretion, occasionally exhibiting a peripheral wedge-shaped area of atelectasis or dense infiltration, and subsequent bronchoscopic removal of the concretion offers a favorable prognosis in an otherwise puzzling and distressing malady.

Congenital cystic lung is a rare anomaly. The few cases surviving infancy offer interesting studies. The literature is filled with conflicting terms for the same congenital anomaly, congenital bronchiectasis, congenital cystic lung, atelectatic bronchiectasis, honey-comb lung. The various terms probably have arisen in association with the many theo-

ries of origin. A congenital origin seems the most plausible, and most easily explains the great number of cystic lungs found in still births and young infants. Congenital cardiac and skeletal lesions are frequent accompaniments. Cysts encountered in adults are usually altered by infection and their origin is difficult to determine, but Koontz noted that a lack of pigment in the tissue involved showed that the part never functioned and is evidence again that the condition antedated birth. Most writers agree on a congenital origin, but its cause is altogether obscure. As to cysts, there are two types reported, the large solitary and the small multiple. The terms above would seem to apply more aptly to the multiple. The two types seem closely related and probably both have a similar congenital origin. The two have occurred together in the same patient, and are probably merely a different expression of the same condition. Some contain fluid when first noticed; in one large solitary cyst of the left lower lobe reported in an infant, the fluid was spontaneously coughed up and the cyst became filled with air. Multiple cysts similarly at first may contain fluid, the fluid later being replaced by air when bronchial communication occurs during development and growth of the lung.

Recognition of the larger solitary cysts is not difficult in the face of severe symptoms. Recurrent attacks of dyspnea and cyanosis in an infant with hyperresonance and displacement of the mediastinum should suggest a cyst rapidly filling with air. Roentgenologic examination should confirm the diagnosis, either alone or with the aid of lipiodol. Small multiple cysts are less easily picked up and, if no infection supervenes, may remain silent in the adult, when diagnosis is unimportant. Infection in infants simulates bronchiectasis with cough and sepsis. There may be little or no sputum. Prognosis is poor, and death ensues usually within the first few weeks or months following birth. Thorpe[12] presented a 10-year record of the small multiple cyst type, a chance Roentgen finding in a routine school examination in which investigation revealed previous roentgenographic examination in infancy. At that time there was infection with cough and fever and the diagnosis was congenital bronchiectasis. The case is remarkable from the fact that the involvement was in an accessory lobe. The patient, a Japanese girl, aged 13, was referred for a Roengen examination of the chest. The clinical diagnosis was tuberculosis. Her complaint was a mild chronic non-productive cough and underweight. In the 10 years since she was first examined she had an intermittent dry cough, her history showed she had spasms of cough without sputum at the age of 2 years, and an attack of whooping cough shortly after birth suggested early manifestation of an anomaly. A roentgenogram of the chest revealed the same multiple air-containing cysts in the right lower lobe noted in March, 1924. They occupied a triangle medially and opposite the heart laterally, so that the normal lung surrounded the cystic area. Their lateral limit was a straight sharp line with slight tenting at its junction with the diaphragm. The heart was not displaced. Roentgenoscopy revealed a slight lag of the diaphragm on the right. Cough elicited no noticeable winking of the cysts.

Reitter[8] presented a case of a white girl, aged 9, whose mother stated that the child had always had some cough, productive at times. The child was referred with a clinical diagnosis of pulmonary tuberculosis, and never had whooping cough, pneumonia or any other acute respira-

tory infection. Physical examination showed clubbing of the fingers and marked pulmonary osteoarthropathy. Roentgenographic examination showed multiple globular cavitations throughout both lungs, with considerable infiltration along the bronchi. Eight Mantoux tests were all negative. Postural drainage produced greenish-mucopurulent sputum on only one occasion tinged with blood. The diagnosis was congenital bronchiectasis.

Acute influenza pneumonitis was applied by Bowen[3] as a term to designate infiltrations localized in various portions of the lung observed in routine Roentgen examinations of patients with mild cases of influenza in the military hospitals in Hawaii. The interesting feature of his roentgenographic reproductions is the simulation of numerous types of lesion including bronchiectasis, abscess, primary and metastastic malignancy. Resolution was the rule in from 7 to 10 days. The typical patient recovered in a few days but routine roentgenographic chest examination revealed a very high incidence of this localized involvement.

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## PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 16, 1936

**Correlated Morphological and Regional Differences in Brain Cultures.**—S. CULVER WILLIAMS (Laboratory of Anatomy, University of Pennsylvania). Tissue cultures in hanging drops of diluted chicken

plasma-embryonic extract were made from mapped regions of the hindbrain of 5-day incubated chick embryos. A study of over a thousand such cultures from 86 brains showed that three regions in each half of the medulla were distinguishable by the character of their behavior.

That part of the medulla anterior to the level of exit of the fifth cranial nerve gave cultures from which for 5 days the outgrowing nerve fibers were relatively straight, moderately branched, and with most branches diverging from one another at a small angle. This region comprises a thick basal plate and a thinner alar plate. Cultures from the basal plate usually show a thining of the explant which exposes structures within it, while from the alar plate, cultures are less apt to thin out.

Cultures from the medulla behind the region of exit of the seventh cranial nerve more frequently show winding highly branched fibers, with many branches diverging widely from one another.

Assuming the culture medium to be the same for all cultures, such differences in morphology may be due to inherent conditions that differ in regional distribution within the brain, for the possibility of external influences from normal growing tracts of fibers nearby has been eliminated.

Some of the differences noted may be ascribed to the behavior of the ameboid growth cone at the active tip of the extending fiber, which is apparently a particularly sensitive portion of the cell surface. Some differences may be related to the fact that the basal plate includes many motor cells, while in the alar plate are many sensory cells.

Whatever the inherent factors responsible, enough are retained under cultural conditions to give recognizable morphological distinctions.

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**Further Studies on the Effect of Section of One Peroneal Nerve of the Albino Rat on the Intact Nerve of the Opposite Side.**—Kozo Tamaki (Wistar Institute, University of Pennsylvania). In a previous study (1933), it was found that section of one peroneal nerve in the albino rat arrested the formation of myelinated fibers in the contralateral nerve, sometimes causing even a loss.

The present study was made to determine how the age of the rat at operation or the prolongation of the interval between operation and killing affected the results.

It was found that the number of myelinated fibers in the tests was always less than in the corresponding controls. With the advancing age at operation, this effect became more marked, while with the increase of the interval after operation, it diminished, thus indicating recovery.

The increases in the sectional areas of the entire nerve were also recorded. The same relations as for the number of fibers were found for the areas.

Thus section of the peroneal nerve on one side of the rat modifies the constitution and the area of the contralateral nerve; but this reaction is in turn modified by the age of the rat at operation and by the length of the postoperative interval. These effects are considered as brought about by toxic substances formed by the damaged neurons, and acting on the corresponding neurons in the opposite side of the cord.

**A Convenient Method for the Determination of the Approximate Cardiac Output in Man.**—JOHN S. DONAL, JR. (Laboratory of Pharmacology, University of Pennsylvania). The purpose of this investigation was to design a cardiac output method more simple than any now in use, and to test its accuracy by comparison with more complicated procedures.

Previous investigators have estimated the oxygen content of the venous blood in man by attempting to secure complete equilibrium between the blood and lung air. The unavoidable dilution of any rebreathed mixture by the residual air makes this process difficult and uncertain and the numerous analyses involved are time-consuming. A method has therefore been developed in which approximate equilibrium with the venous blood is attained in a single rebreathing of about 2500 cc. of nitrogen. Two accurately timed samples, taken after mixing is complete and before recirculation begins, permit the calculation of the cardiac output from the formula:

$$\text{Cardiac output} = \frac{(A-B)}{(C-D)}$$

where A is the oxygen consumption in cc. per minute, measured in the usual manner; B is the oxygen consumption in cc. per minute during the rebreathing period between the collection of samples; C is the normal arterial oxygen content, or 96% of the blood oxygen capacity, as estimated from a hemoglobin determination; and D is the oxygen content of arterial blood as calculated from the average of the tensions of oxygen and carbon dioxid in the two alveolar samples and a standard nomogram.

The oxygen consumption, B, found during the rebreathing of nitrogen, is calculated from an assumed volume of residual air which is not accurately estimated. It should also be corrected for the unknown change in circulatory rate resulting from rebreathing. B is small compared to A, however, and it has been found that these errors do not greatly affect the calculated cardiac output.

Estimations of basal cardiac output by this procedure have been found to be in good agreement with determinations made on the same subjects by the ethyl iodid method of Starr and Gamble and by the acetylene method of Grollman.

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**A Circulation Schema, with Pumps Obeying Starling's "Law of the Heart."**—*I. The Construction of the Schema from Physiological Data. II. On the Causes of Increased Venous Pressure, in the Schema, and in Certain Clinical Conditions.* ISAAC STARR, JR., and A. J. RAWSON (Department of Research Therapeutics and Johnson Foundation, University of Pennsylvania). A circulation schema has been constructed, with pumps which fill without suction and put forth more work the more completely they are filled; *i. e.*, their behavior simulates Starling's Law of the Heart. In this schema the factors responsible for increases of venous pressure as the "heart" is weakened can be divided into two main classes by their relationship to the general systemic pressure, *i. e.*, the pressure existing throughout the system when the pump is stopped. Thus if increased "venous" pressure is caused by appropriate alteration of the resistances, or by weakening one side of the heart, venous pressure falls when the heart is stopped. If increased

venous pressure is due to a diminution of the reduction of pressure, which can be demonstrated on the "venous" side of any circulation when a single pump is started, the venous pressure will rise when the pump is stopped. If an increased venous pressure is due to an elevation of the general systemic pressure, the venous pressure remains elevated after the pump is stopped.

The reduction in cardiac output following weakening of the "heart" can be compensated by increasing the general systemic pressure in our schema.

In the clinic, we have attempted to analyze the factors causing increased venous pressure by comparing this pressure during life with the pressure prevailing throughout the circulation immediately after the cessation of cardiac action. The latter pressure remains very constant for at least 1 hour after death. Ten cases never known to have had increased venous pressure during life had general systemic pressures, ranging from 11 to 0, average 4.6 cm. $H_2O$ after cessation of cardiac action. Cases with increased venous pressure during life divide themselves into two classes. For example, in a man with venous obstruction, the pressure fell from 50 cm. during life to 4 cm. after death. But in several cardiac cases the increased venous pressure was maintained after death at a point very close to its level during life.

The results suggest that these cardiac cases had an increased general systemic pressure, perhaps to compensate for cardiac weakness, and that this is an important factor in the increased venous pressure they exhibited during life.

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